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EFFECT OF TESTOSTERONE ON THE EXCRETION OF GLYCOGENIC CORTICOIDS

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ANIMAL experimentation by numerous investigators has shown that the administration of testosterone to intact rats has a definite effect on the anterior pituitary as well as on other glands of internal secretion such as the adrenal, the thyroid, the testes and the ovary (5, 6, 9, 10, 11, 12, 13, 17). In rats testosterone propionate will cause atrophy of the pituitary gland and involution of the adrenal gland; the latter occurring more readily in female rats than in males (6, 10).

Reifenstein and co-workers (8) have reported that the administration of methyl testosterone to humans will cause a decrease in the excretion of 17-ketosteroids of adrenal origin. It seemed of interest therefore to determine whether testosterone would have an inhibiting effect on other types of adrenal metabolites, particularly those associated with carbohydrate metabolism, namely the glycogenic corticoids. The present paper is concerned primarily with the effect of testosterone propionate and methyl testosterone upon the excretion of these substances. Simultaneous studies on the excretion of 17-ketosteroids were also made.

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METHODS

Investigations were carried out on eight individuals: 3 normals, 2 patients with diabetes mellitus, 1 with lupus erythematosus disseminatus, and 2 with Cushing's syndrome. Complete 24-hour specimens of urine were collected on all patients before and during testosterone therapy. The urine was pooled in lots of 48-hour or 72-hour amounts and aliquots were used for the determinations. The accuracy of the collection of urine was checked by creatinine determinations. All results are reported in terms of amounts excreted per 24 hours. The glycogenic corticoids were assayed according to the bioassay method of Venning, Kazmin and Bell (15) which is dependent upon the deposition of glycogen in the livers of adrenalectomized mice. The results are expressed in terms of glycogenic units, one unit being equivalent to the activity of 1 microgram of 17-OH-11-dehydrocorticosterone. The normal excretion range for men is from 40 to 90 glycogenic units per 24 hours and for women from 25 to 70 glycogenic units per 24 hours.

The urinary 17-ketosteroids were measured by means of the colorimetric method of Holtorff and Koch (3) and a color correction was applied.

Testosterone propionate was injected intramuscularly and methyl testosterone was administered orally in the form of tablets.

CLINICAL MATERIAL AND RESULTS

Case 1 (Fig. 1). A woman aged 45 years, had no disease and a normal output of glycogenic corticoids and 17-ketosteroids. Measurements were made on 72-hour urine collections. In the two control periods the urinary corticoids were 42 and 45 units per 24 hours. Twenty-five mg. testosterone propionate were administered daily for 6 days. There was an initial increase in output of glycogenic corticoids which might possibly be accounted for by the fact that the individual developed a head cold at this time. However, the cold cleared up within a few days and at the end of the therapy the glycogenic corticoids had decreased to a level of 29 units per 24 hours. One week later, they had returned to their original level. As testosterone propionate is metabolized to 17-ketosteroids, the usual rise in urinary 17-ketosteroids is seen following the administration of this hormone.

Case 2 (Fig. 1). A man, aged 55 years, had no disease, but the 17-ketosteroids in two control periods were 8.7 and 7.0 mg/24 hours—below the normal range. Determinations were made on 72-hour collections. The glycogenic corticoids were 85 and 87 units/24 hours. Forty mg. of methyl testosterone were administered orally over a period of 10 days. Then the dosage was reduced to 10 mg. for a further period of 17 days. At the end of the tenth day after 40 mg. of methyl testosterone the glycogenic corti-

coids were depressed to a level of 35 units/24 hours. On the lower dose of 10 mg. they increased somewhat to a level of 45 units/24 hours. The 17-ketosteroids had gradually decreased to a low level of 3.8 mg./24 hours by the tenth day, but increased again to 6.1 mg. when the dosage of methyl testosterone was reduced.

Case 3 (Fig. 2). A male, aged 21 years, had no disease. Numerous assays of urinary glycogenic corticoids showed a consistently higher excretion than that of other normal males in this age group. Determinations were

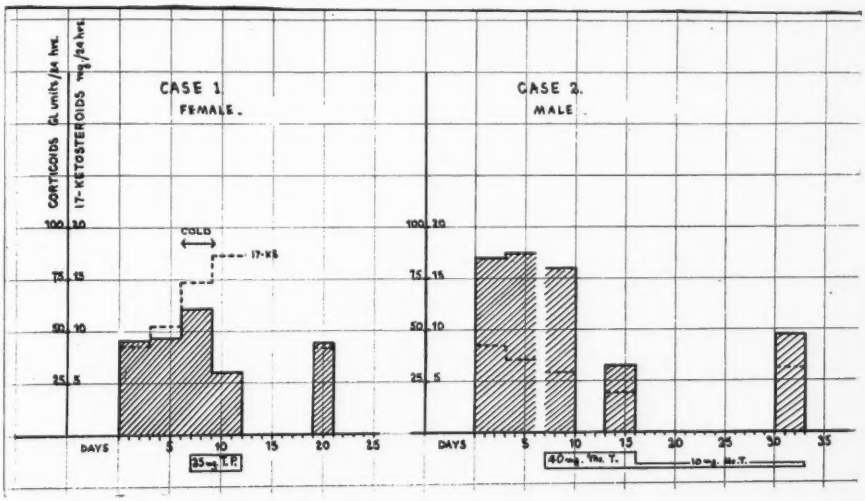

FIG. 1. Effect of testosterone propionate and methyl testosterone on the excretion of glycogenic corticoids and 17-ketosteroids in two normal individuals. The hatched columns represent the corticoids and the interrupted line the 17-ketosteroids.

made on 48-hour collections. In the two control periods, the glycogenic corticoids were 110 and 115 units/24 hours, the 17-ketosteroids 21 and 23 mg./24 hours. Fifty mg. of testosterone propionate were administered daily for a period of 6 days. Under this treatment the level of glycogenic corticoids gradually fell, reaching a low value of 40 units/24 hours.

Case 4 (Fig. 2). A woman, aged 25 years, had diabetes mellitus. This patient was given 20 mg. of methyl testosterone orally for 5 days. Before therapy the urinary corticoids were 73 units/24 hours. With methyl testosterone the excretion rate decreased to 37 units and one week later it had risen to 83 units. The 17-ketosteroids were depressed from 9.5 mg/24 hours to 6.0 mg./24 hours. One week after cessation of therapy they were 14 mg./24 hours.

Case 5 (Fig. 3). A young girl, aged 14 years, suffered from lupus erythematosus disseminatus. During the period of study the patient's temperature ranged from 99° to 102.4°F. Assays were made on urine collections of 48 hours. Two control periods approximately 2 weeks apart showed increased corticoid excretions of 98 and 93 units per 24 hours. The 17-

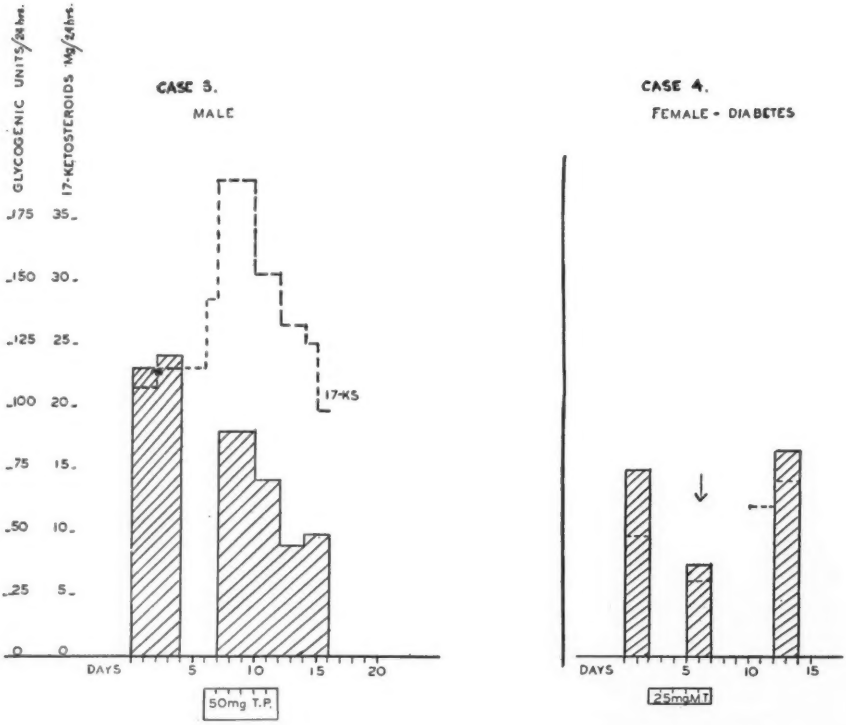

FIG. 2. Effect of testosterone propionate and methyl testosterone on the excretion of glycogenic corticoids and 17-ketosteroids.

ketosteroids averaged 4.6 and 5.5 mg./24 hours. With the daily administration of 50 mg. of testosterone propionate, the corticoids decreased to 40 units/24 hours on the fourth and fifth days, and to 29 units/24 hours on the 8th and 9th days. On the 14th and 15th days of therapy, the corticoids were 29 units/24 hours. The excretion of 17-ketosteroids rose with the testosterone propionate therapy to a high level of 21 mg./24 hours, but this was not maintained in spite of continued injections of testosterone propionate, suggesting that the endogenous supply of 17-ketosteroids was

being suppressed. There was no change in temperature or in the clinical condition of the patient during the period of study.

Case 6 (Fig. 3). A woman, aged 40 years, had diabetes mellitus associated with hirsutism. Excretion of 17-ketosteroids and glycogenic corticoids was normal. A low blood sodium, pigmentation of the skin and hypotension suggested underfunction of the adrenal with regard to regulation of electrolyte metabolism. Three separate assays of corticoids gave values of 55,

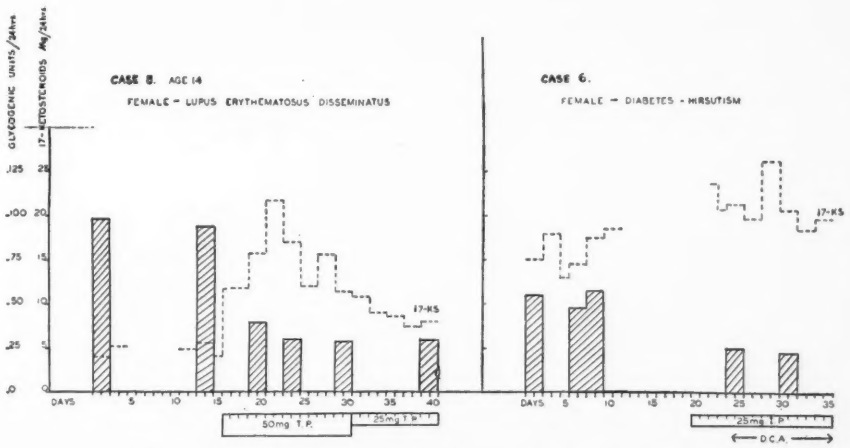

FIG. 3. Effect of testosterone propionate on the excretion of glycogenic corticoids and 17-ketosteroids.

49, and 57 glycogenic units/24 hours respectively. With the administration of 25 mg. of testosterone propionate, the corticoids were depressed to levels of 22 and 25 units. Five mg. desoxycorticosterone were administered daily beginning on the 6th day of testosterone therapy, but failed to cause any further depression of the urinary corticoids.

Case 7 (Fig. 4). The patient was a woman, aged 42 years, with Cushing's syndrome. She was studied over a control period of 13 days. The 17-ketosteroids averaged 20 mg./24 hours and the glycogenic corticoids 260 units/24 hours. On the 14th day, 25 mg. testosterone propionate were administered daily for 13 days and then twice weekly for five weeks. The adrenals were irradiated for two weeks between days 20 and 36. On the 3rd and 4th days of administration of testosterone propionate, the corticoids decreased to 88 units. They remained at a low level throughout the treatment, varying between 55 and 70 units/24 hours. The 17-ketosteroids increased initially with the administration of testosterone propionate, but gradually fell with continued treatment until the 36th day, after which

they increased again to their original level. A glucose tolerance test made on the 3rd day showed marked impairment. When repeated on the 66th day after 7 weeks of treatment with testosterone propionate, the curve was normal. These are shown in Fig. 5.

Case 8 (Fig. 6). A man, aged 32 years, had Cushing's syndrome. Increased appetite and thirst during the past five years resulted in a striking increase in weight to 351 lbs. "Appetite rages," repeated "absences," sleep

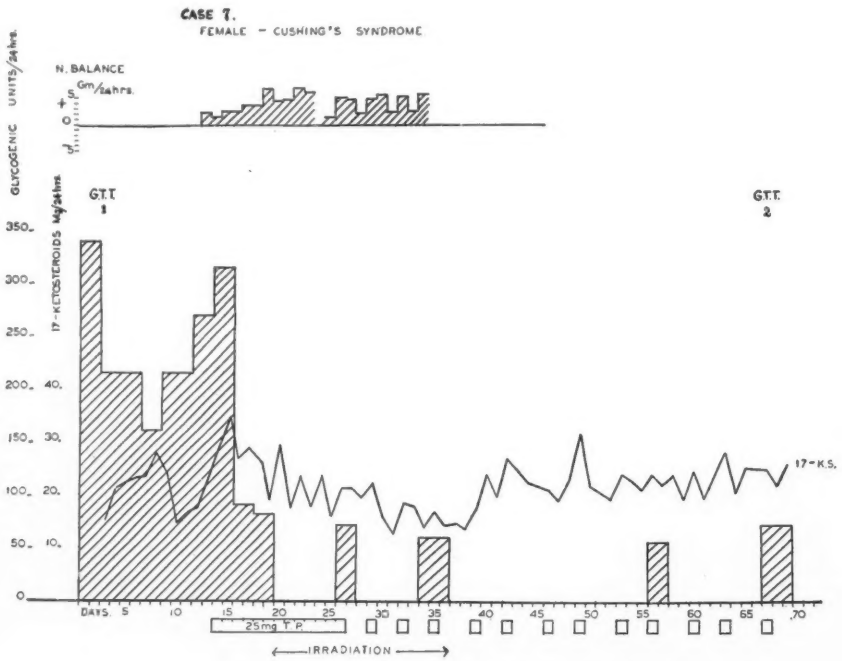

FIG. 4. Effect of testosterone propionate on the excretion of glycogenic corticoids and 17-ketosteroids in a woman with Cushing's syndrome.

disturbances, abnormal waves in basal lead of the electroencephalogram, and the result of a pneumoencephalography suggested a hypothalamic lesion. The glycogenic corticoids ranged from 356 to 546 units per 24 hours and the 17-ketosteroids from 10 to 16 mg. per 24 hours. Twenty-five mg. testosterone propionate were administered daily from the 21st day of study until the 51st day, when the dosage was increased to 50 mg. During the first 6 days of administration of testosterone propionate, on days 21 to 26, no effect on the glycogenic corticoids was seen. On days 27 to 36, the excretion of corticoids decreased to 250 units but later increased again with con-

tinued testosterone therapy. When the dosage was increased to 50 mg. no change in the excretion of glycogenic corticoids occurred. Glucose tolerance tests carried out at various intervals, showed increasing impairment of function as shown in Fig. 7.

DISCUSSION

Although the number of cases studied in this series is admittedly small, in all but one the administration of either testosterone propionate or methyl testosterone caused a decrease in the excretion of glycogenic corti-

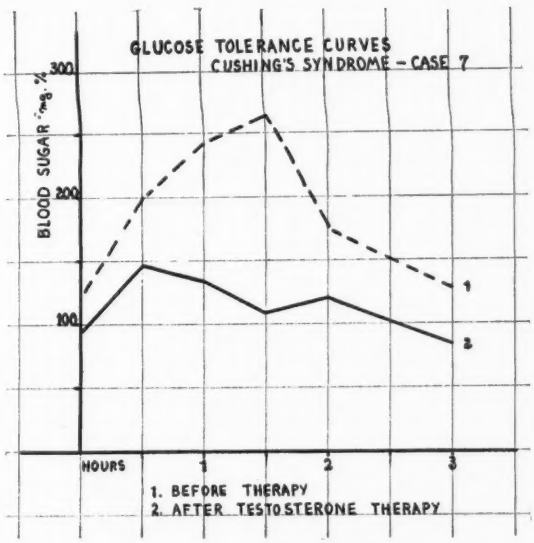

FIG. 5. Glucose tolerance curves in *case 7*, a woman with Cushing's syndrome before and 53 days after testosterone therapy.

coids. That this depression is not fortuitous but related to the therapy is borne out by time relationships between the treatment and decline of level of excretion of glycogenic corticoids. Within two to three days after the beginning of the administration of testosterone a definite decrease in excretion rate was noted. Only in *case 2* where methyl testosterone was given was there some lag in the effect. In this case, however, by the 7th, 8th and 9th days a decrease was also observed. The average decline in excretion of corticoids in the first 6 cases was 55 per cent. In *cases 1* and *6*, receiving 25 mg. of testosterone propionate, the corticoids decreased 33 and 45 per cent, while in *cases 3* and *5*, receiving twice the amount of testosterone

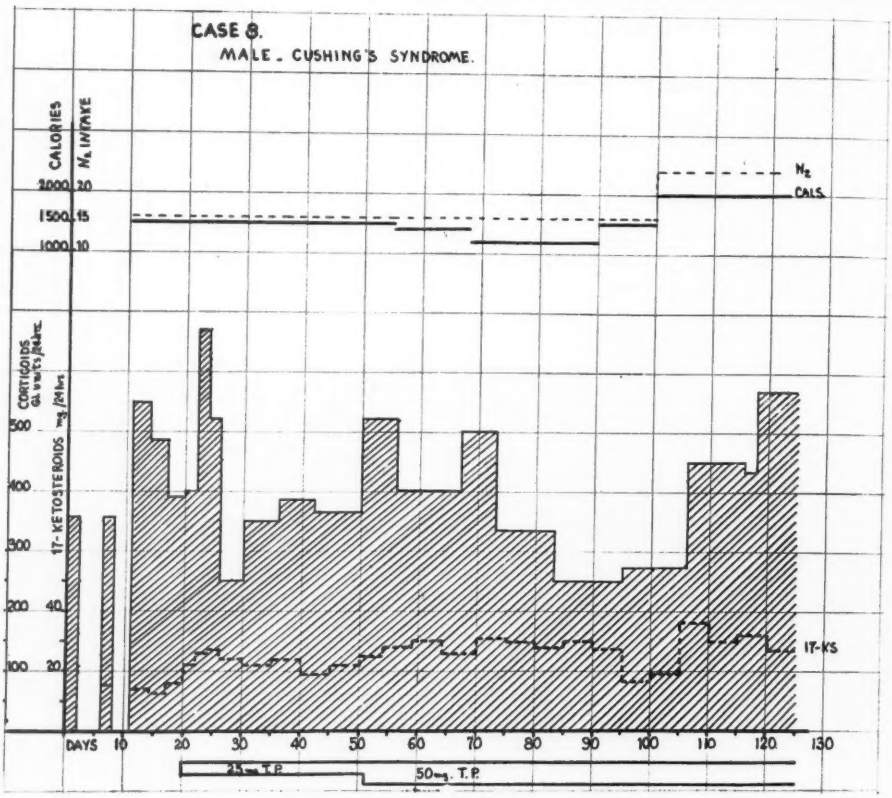

FIG. 6. Excretion of glycogenic corticoids and 17-ketosteroids in a man with Cushing's syndrome.

propionate, they decreased 60 and 75 per cent. These two patients, however, had higher control values of urinary corticoids. The patient with Cushing's syndrome (*case 7*) with a markedly increased rate of excretion of 260 units/24 hours, showed the greatest depression with 25 mg. testosterone propionate. This inhibiting effect of testosterone upon adrenal metabolism is not a permanent one as seen in *cases 1* and *4*. Within approximately a week of cessation of treatment the glycogenic corticoids and 17-ketosteroids were back to their initial levels. It is interesting to note that in *case 5* the high excretion of corticoids, probably due to a response of the adrenal to infection, was markedly reduced by testosterone therapy even though the fever persisted with temperatures ranging from 100° to 102°F.

One significant fact brought out by these studies is that with the dosages

given it has not been possible to lower the corticoid excretion much below the lower limit of normal excretion for the individual concerned, 40 units for males and 25 units for females. With regard to the effect of methyl testosterone on the excretion of 17-ketosteroids, the results in *cases 2* and *4* confirm the findings of Reifenstein and co-workers (8) that this hormone will definitely lower the excretion of 17-ketosteroids. When testosterone

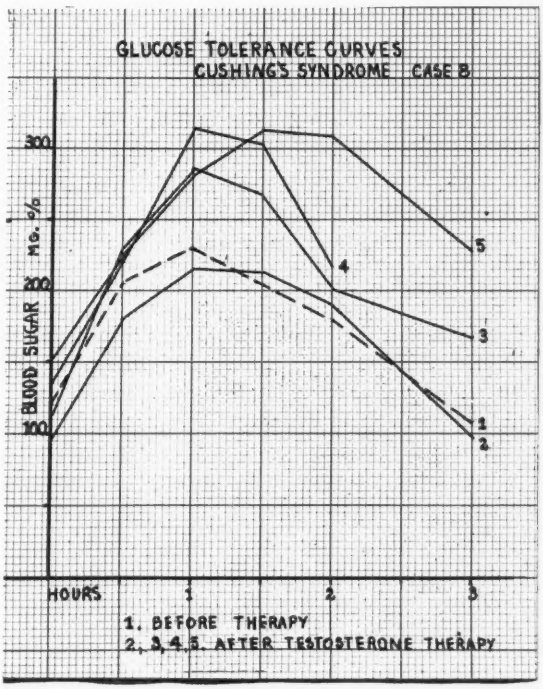

FIG. 7. Glucose tolerance curves in *case 8*, a man with Cushing's syndrome (1) before treatment, (2) after 31 days, (3) 72 days, (4) 127 days and (5) 214 days of testosterone therapy.

propionate is given, the added metabolites from the administered hormone, in the form of 17-ketosteroids, obscure the results. However, it is observed that in many of the cases with continued administration of testosterone propionate the level of 17-ketosteroids tends to fall, thus suggesting that those derived from endogenous sources are being depressed.

It was found that in *case 7*, a woman with Cushing's syndrome, it was possible to maintain the glycogenic corticoid excretion within normal limits

with administrations of 25 mg. testosterone propionate twice weekly. The changes that occurred in the glucose tolerance curves were most significant. Before therapy, at a time when the glycogenic corticoid excretion was high, average value of 260 units/24 hours, the test showed an impaired tolerance curve; after 5 weeks of therapy with testosterone propionate, both glucose tolerance and glycogenic corticoid excretion were normal.

In contrast to this we find that in *case 8*, a male, also with Cushing's syndrome, failed to show any continued effect of testosterone therapy. There was a decline in the corticoid excretion from 670 units to 250 units over a period of 10 days following the daily administration of 25 mg. of testosterone propionate, but this was not maintained and the excretion rose again. When the testosterone propionate was increased to 50 mg. no effect was observed. The glucose tolerance curves showed increasing impairment in function throughout the study, and their character was not altered by testosterone therapy (Fig. 7).

There appears to be little in the physical and clinical histories of these two patients with Cushing's syndrome to suggest why one should respond to testosterone therapy and the other one fail to do so. The onset of the disease in *case 8* had been more rapid and much more severe than in *case 7*, and it may be possible that the pathological lesion responsible for the disease in *case 8* was more difficult to influence than that in *case 7*. In earlier work regarding the effect of testosterone on adrenal atrophy, it was observed that the response was more readily obtained in female than in male rats (6, 10). However, in the two studies on male individuals with no disease, *cases 2* and *3*, it was possible to show that both testosterone propionate and methyl testosterone were effective in causing a reduction in excretion of adrenal metabolites. The three patients with Cushing's syndrome, successfully treated with testosterone propionate as reported by Albright et al. (1), were all women as was the patient reported by Perloff et al. (7), who noted an improvement in the tolerance for dextrose after prolonged testosterone therapy. The patient of Deakins et al. (2), a 15 year old girl with Cushing's syndrome, failed to show demonstrable clinical improvement with testosterone propionate and methyl testosterone despite the definite effect which these hormones were shown to have had upon her nitrogen balance. Whitelaw (16) reported that a 17 year old boy with the same disease, under testosterone propionate therapy showed no improvement in the osteoporosis or tolerance for glucose although there was a marked gain in strength and weight and an increased excretion of creatine.

What is the mechanism of the action of testosterone upon adrenal metabolism? Is this inhibiting effect a direct action of testosterone itself upon the adrenal or is it a result of the suppression of those tropic hormones of the anterior pituitary which control adrenal metabolism?

Proof that this effect is mediated through the pituitary has been supplied by the work of Selye (10) who has shown that in hypophysectomized rats maintained on adrenotropic hormone, testosterone fails to cause atrophy of the adrenals. Reifenstein and co-workers (8) have put forth evidence to support the theory that the tropic hormone responsible for the production of 17-ketosteroids from both the testis and the adrenal is the luteinizing hormone. The more recent work of Thorn, Prunty, and Forsham (14) and of Mason and co-workers (4), however, on the effects of purified adrenotropic hormone reveals that this pituitary hormone will also stimulate the production of 17-ketosteroids as well as 11-oxysteroids. An interference with the production of adrenotropic hormone alone by the administration of testosterone could, therefore, equally well account for the reduction in excretion of both glycogenic corticoids and 17-ketosteroids.

The beneficial effect of testosterone propionate therapy in Cushing's syndrome may therefore be due not only to the metabolic action of testosterone directly opposing the effect of the glycogenic type of corticoid on protein and carbohydrate metabolism as suggested by Albright but also in certain cases to a repression of the over-activity of the adrenal cortex.

SUMMARY

The excretion of urinary glycogenic corticoids and 17-ketosteroids was followed in a series of 8 individuals before and after the administration of either testosterone propionate or methyl testosterone. These included 3 normals, one woman and 2 men; 2 women with diabetes; one young girl with lupus erythematosus disseminatus; and 2 cases of Cushing's syndrome, one male and one female.

In all the cases, with the exception of the male with Cushing's syndrome, testosterone therapy caused a reduction in the rate of excretion of glycogenic corticoids.

In the cases under methyl testosterone therapy a decrease in urinary 17-ketosteroids was also noted. It is suggested that this inhibition caused by testosterone therapy is mediated through the pituitary by the reduction in production of adrenotropic hormone.

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TRUE HERMAPHRODITISM

ENDOCRINE STUDIES IN A CASE OF OVOTESTIS

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THE occurrence of both male and female gonads in one person is of sufficient rarity to invite thorough study of such a case. Pseudohermaphroditism is not uncommon, but the occurrence in one person of one ovary and testis, or an ovotestis, proved histologically, has been reported only 40 times in the literature (1, 2, 4, 5, 6, 7). Excellent reviews of true hermaphroditism have been written by McIver and associates (4) and Young (7). In both of these reports the predominant abnormality was the presence of ovotestes, either unilateral or bilateral. Only seven true ovaries were found in the series, and six true testes; the remainder (except for four gonads of undetermined type) were ovotestes. The clinical features of these cases were such as to cause suspicion of hermaphroditism with insufficient development of the attributes of either sex. The rarity of this condition warrants the report of such a case in detail.

REPORT OF CASE

D. M. (*T-46-226172*), a negro "female," aged 36, was admitted to Charity Hospital in New Orleans on July 18, 1946, because of a "mass between her legs," which had been present as long as she could remember, but which had recently increased so much in size as to cause local discomfort.

The patient was one of twins and was considered a female at birth. From the history, it would seem that at birth a small lump was present in the perineum beneath which was the urethral orifice. Apparently, the patient's mother had no reason to suspect an abnormality and the child was reared as a sister to the other girls.

Adolescence began between the tenth and twelfth years. Development followed the female pattern, with mammary glands enlarging to a degree comparable to the patient's twin sister. Mammary development continued until the twentieth year, when slow regression began. "Menstruation" began at the age of 11 years, with regular cycles, at 28 to 30 day intervals. The flow was said to be scanty and lasted one and a half days. The site from which the flow emerged was unknown to the patient, who was unconcerned about the anatomic abnormalities. Mild abdominal cramps accompanied the menses for about five years after the menarche. Axillary and pubic hair developed in feminine fashion with little or no overgrowth in the earlier years. From the twentieth year, facial

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hair on the upper lip and chin began to appear, and some increase was noted along the linea nigra of the abdomen. There was no vocal change and at present the patient sings soprano in a choir. As the patient grew, the mass enlarged becoming more prominent on the right side until its present size prompted her to seek medical advice.

FIG. 1. Photograph of patient showing general body development.

The patient's thoughts and actions were always mediated by the conviction that she was a female. She preferred the company of men and had several beaux. Marriage was contemplated at one time, but her fiancé was accidentally killed. Although she had frequent dates, she denied any attempts at sexual activity.

The patient had four brothers and two sisters all of whom were normally developed; the two sisters were married, and one was the mother of two normal children.

Examination revealed a well nourished negro "woman" weighing 112 pounds, 65¼ inches tall, with a span of 68 inches. Facial hair with masculine distribution was sparse but conspicuous. The breasts were well developed but atrophic changes were evident. A large inguinal hernia on the right side with considerable chronic edema of the sac protruded about 10 to 12 cm. from the level of the pubic tubercle; it was not completely reducible (Fig. 1).

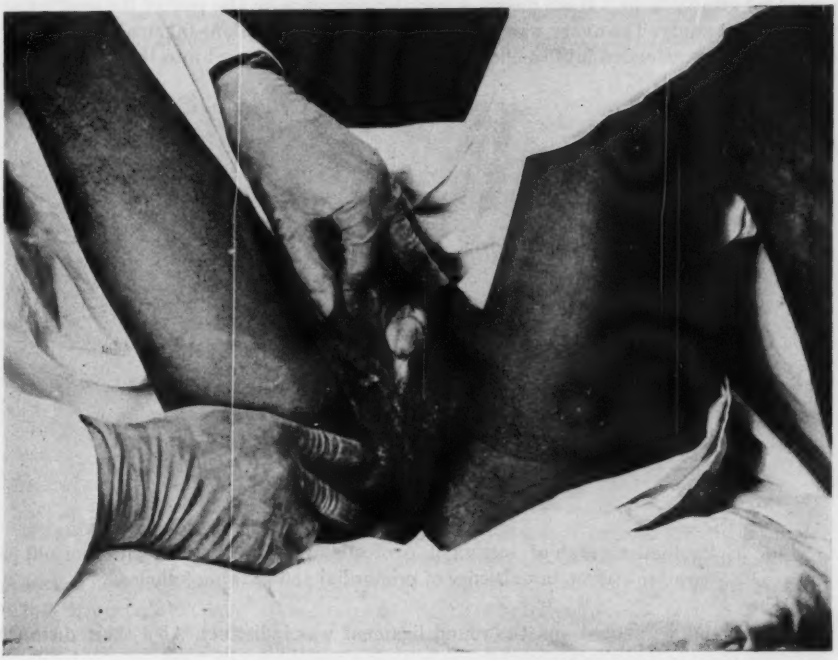

FIG. 2. Photograph of patient's external genitals.

The external genitals were neither masculine nor feminine. There was a large phallus, measuring approximately 3 cm. in length (Fig. 2). Its prepuce disappeared into the pubic skin without forming any rudimentary labia minora. No labia majora could be identified and there was no scrotal swelling. The urethral orifice was situated about 1 cm. dorsal to the base of the phallic structure. Rectal examination revealed a granular tag which bled easily upon trauma. No rudimentary structures comparable to a prostate gland or müllerian system could be felt on palpating the anterior rectal wall. Cystoscopic examination revealed a normal female urethra without a vaginal orifice or a verumontanum.

A plain roentgenogram of the kidney, ureter and bladder showed essentially normal structures. Roentgenologic examination of the skull disclosed indistinct posterior clinoid processes but no other abnormalities.

Preoperatively, urinary gonad-stimulating hormone assays showed >96 <192 M.U./24 hrs., and >52.8 <100 M.U./24 hrs.; 17-ketosteroid determinations were 7.6

and 7.5 mg./24 hrs. The urinary gonad-stimulating hormones were estimated by the uterine weight method of Klinefelter, Albright and Griswold (3) and the 17-ketosteroids by a modification of the Zimmerman reaction with dehydro-iso-androsterone as a standard.

On July 26, 1946, under spinal anesthesia, the right inguinal hernia was repaired. The sac contained omentum incarcerated with a sliding hernia of pelvic organs. There was a rudimentary uterus with a well developed left fallopian tube and a left gonad which appeared grossly to be a small ovary. A nodular eminence on one pole of the ovary was removed for study. The ovary was bisected and a slice of tissue was taken also for study. The right tube extended into the herniated mass and disappeared into the sac wall. No

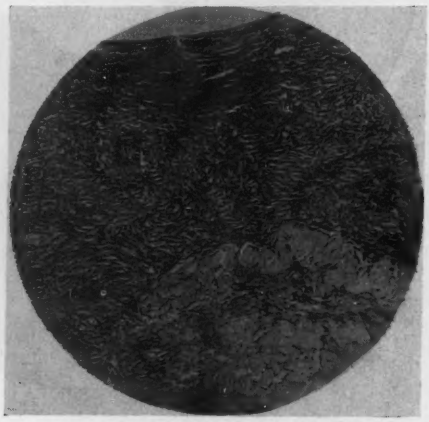

FIG. 3. Photomicrograph of section of ovotestis (ovarian portion) with normal ovarian stroma but absence of primordial and growing follicles.

fimbriated end was noted and the round ligament was indistinct. At a short distance from the point of disappearance of the right tube a nodule, 2.5 by 1 cm., was palpable in the sac; this nodule did not have a free border and did not simulate the right gonad grossly. No gonad was seen. The omentum was free, and the redundant sac, with the nodule, was severed from the rudimentary uterus. The hernia was repaired, and the granular anal tag was also removed. It was felt that this might contain aberrant endometrial tissue from which cyclic bleeding occurred.

On August 10, 1946, a plastic operation was performed. The redundant skin was used to form a vagina behind the urethral orifice. Subsequently, the greater portion of this whole thickness graft sloughed away. The vagina was maintained with an obturator for a time but has since contracted to a mere sinus tract. A further plastic operation will be needed.

The postoperative course was entirely uneventful. Five weeks after the operation 17-ketosteroids were determined on three occasions and, the amounts were 5 mg./24 hrs., 4.9 mg./24 hrs., and 5.6 mg./24 hrs. The urinary gonad-stimulating hormone was assayed in two of these 24-hour urine collections, both assays containing $>96<192$ M.U. /24 hrs. After nine months, the patient is still in good health and further "menstruation" has not occurred.

Histologic examination of the hernial sac revealed an ovotestis protruding from the lining. The larger portion of the gonad was well differentiated ovarian stroma, with several large corpora albicantia (Fig. 3). No growing follicles or ova were observed in the sections available, but there was a Walthard cell rest close to the surface in one section.

The testicular portion of the gonad was located on the deeper surface, corresponding to the medullary border. There were definite testicular tubules, well differentiated in outline, but in varying degrees of degeneration. Hyalinization and fibrosis were rather marked. No evidence of spermatogenesis could be seen (Fig. 4a). Interposed between

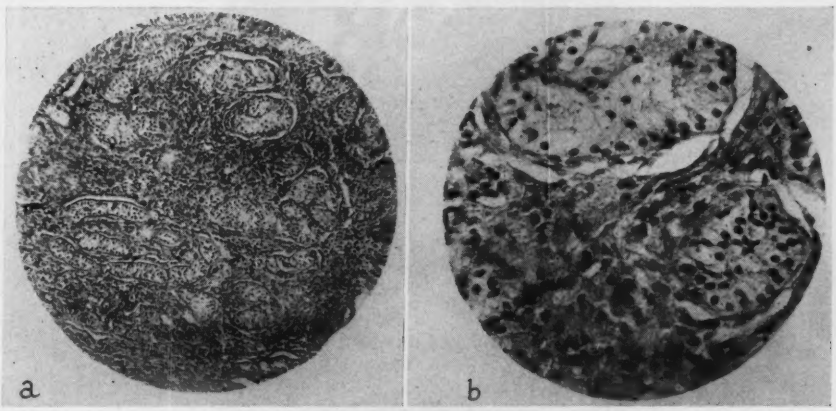

FIG. 4(a). Low power magnification of ovotestis, showing numerous testicular tubules in all stages of degeneration. Spermatogenesis is absent, and hyalinization of many tubules can be seen. Small clumps of interstitial cells are numerous. (b). High power magnification of a tubule showing interstitial cells wedged in between.

tubules, and often in large clumps, were masses of interstitial cells of Leydig (Fig. 4b). A well formed rete testis was present (Fig. 5).

Extending from one pole of the ovotestis was a thickening of the hernial sac which resembled, histologically, the spermatic cord or epididymis, although the differentiation was immature (Fig. 6). A neighboring strand of tissue consisted of fibromuscular tissue, lined with columnar epithelium, which resembled tubal epithelium.

The biopsies of the left ovary consisted of a small portion of normal ovarian stroma, also with corpora albicantia, but no growing follicles or ova. The nodular portion contained a small Brenner tumor surrounded by fibrous stroma showing little hyalinization (Fig. 7).

Examination of the rectal polyp revealed only rectal glands surmounted by stratified squamous epithelium.

COMMENT

This case is one of true hermaphroditism, with a normal ovary on the left and an ovotestis on the right. Of the 40 cases reported in the literature, only 11 were of the lateral or alternating type, with an ovary on one side

and a testicle on the other. Eleven patients had bilateral ovotestes, 7 had ovotestes combined with testes and 7 had an ovary with the ovotestis. Four patients had ovotestes with the other gonad unidentified.

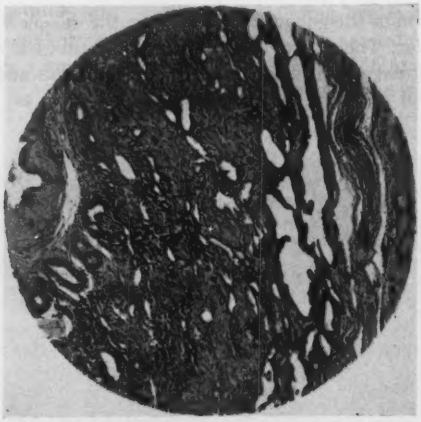

FIG. 5. Low power magnification of section of ovotestis showing well developed rete testis.

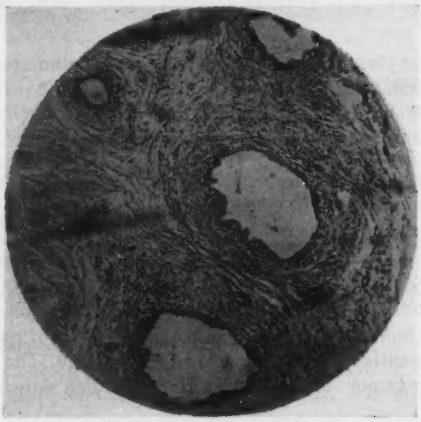

FIG. 6. Low power magnification of section of hernial sac containing fibromuscular tissue, lined with columnar epithelium resembling the epididymis.

The frequency of inguinal hernia in the reported cases (14 of 40 cases) is striking. When associated with any sexual abnormality, inguinal hernia should immediately suggest the presence of intersexuality of some degree.

The principal complaint of this patient was the hernia, not the intersexual status.

Hormonal assays have been performed in only a few of the cases reported. In our case, the 17-ketosteroid excretion was somewhat lower than anticipated. In our laboratory, the range of 17-ketosteroids in the normal female extends from 4.3 to 18.2 mg./24 hrs. with a mean of 8.7 mg./24 hrs. The range for normal males is from 7.2 mg./24 hrs. to 27.2 mg./24 hrs. with a mean of 15.9 mg./24 hrs. The amount excreted in our case is, therefore, among the lower values for the female. The decrease in values

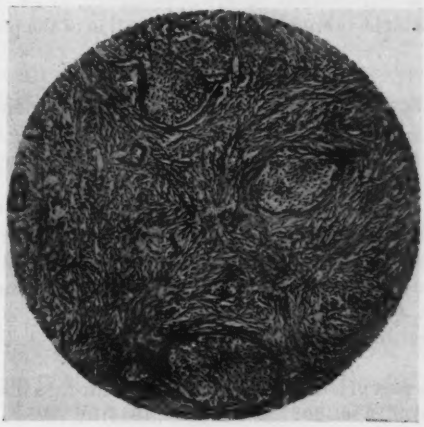

FIG. 7. Low power magnification of section of nodule of left ovary, with small Brenner tumor, consisting of well defined epithelial elements surrounded by fibrous stroma.

obtained postoperatively suggested that a portion of the excreted 17-ketosteroid was derived from the testicular tissue, which was removed, although spontaneous fluctuations in excretion are not uncommon.

We have not seen a normal male or female in whom the urinary gonad-stimulating hormone excretion was as great as the 96 M.U./24 hrs. which this patient showed. It is of interest to note that although the 17-ketosteroid excretion dropped after operation, indicating a loss of hormonally active gonad, this was not borne out by a concomitant rise in urinary gonad stimulating hormone. The relatively high urinary gonadotropic hormone values suggested that gonadal failure existed. The inactivity of the ovarian sections was confirmatory.

SUMMARY

1. A case of true hermaphroditism with an ovotestis on the right and an ovary on the left is presented.

2. Manifestations of normal female sexual development with superimposed facial hirsutism and an enlarged clitoris were distinguishing features.

3. The ovotestis was found in a hernial sac as in 14 other cases in the literature.

4. The 17-ketosteroid excretion was reduced postoperatively; this suggests bio-activity in the testicular portion.

5. The gonadotropic excretion in the urine was elevated indicating gonadal failure.

ACKNOWLEDGMENT

The authors wish to express their sincere appreciation to Dr. William Sternberg for his assistance in the pathologic studies and in preparation of the photomicrographs.

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A COMPARATIVE STUDY OF VAGINAL AND CERVICAL CORNIFICATION IN HUMAN SUBJECTS*

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THE advent of the cervical os smear (1) for the diagnosis of uterine cancer has led to extensive comparative studies of the vaginal and cervical methods in this laboratory. Cervical smears have been found to contain a larger concentration of cancer cells in positive cases. It has also been observed that almost invariably a greater concentration of the estrogenic cornified cells is found in the cervical smear than in the vaginal smear. This observation has prompted a study of the cornification counts of smears from the cervix compared with those from the vagina in 125 patients.

The cases were chosen at random from our files of patients who had had both vaginal and cervical smears taken at the same time. Patients with cancer and those patients who showed total absence of estrogen, e.g., normal senile patients or castrates, were excluded. The smears covered all stages of the menstrual cycle and a large variety of age groups. It was found that 88.8 per cent of the cases showed the cervical cornification count to be higher than the vaginal cornification count, varying from 5 per cent to 55 per cent. Equal cornification levels were observed in 7.2 per cent and 4 per cent showed a higher count in the vaginal than in the cervical smear. (This varied from 5 per cent to 10 per cent.) The over-all average difference between the cervical and vaginal cornification counts was 15.5 per cent.

METHOD

A speculum was used in taking both the vaginal and cervical smears. Selective smears and scrapings were used in preference to a random aspiration. An area of the lateral wall of the vagina was lightly scraped with a wooden spatula and the scrapings were spread over a glass slide. Cervical scrapings were taken using the cervical spatula designed to scrape the squamous margin of the squamo-columnar junction, according to the technique described by one of us (2). The slides were stained with Papanicolaou's polychrome stain.

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Cornification levels are estimated by counting the number of cornified cells per hundred epithelial cells of the squamous type. The result is expressed in percentage and referred to as the cornification count or cornification level. A cornified cell is recognized as much by its morphological as by its staining characteristics. It is defined as a large, flat, wafer-like epithelial cell with a small round or oval pyknotic nucleus. The cytoplasm is acidophilic and therefore shows a pink coloration with the polychrome stain of Papanicolaou. The "pre-cornified" epithelial cells are morphologically similar, but have a basophilic cytoplasm which stains blue-green. Other immature squamous cell-types also take the basophilic stain.

It is important to eliminate cells showing "pseudo-cornification" where an acidophilic staining reaction occurs in a cell showing nuclear morphology of immaturity. Such cells are not included in the cornification count.

It has been shown that the cornification count varies in individual patients with the physiological changes during the menstrual cycle (4, 5). The cornification level rises gradually during the follicular phase, paralleling the production of estrogen by the ovarian follicle and reaches a peak, usually over 50 per cent, at ovulation. The count then drops irregularly during the luteal phase of the cycle to a premenstrual low, approaching zero.

It has been shown that when estrogen is given orally or by injection to post-menopausal and castrate women the cornification level rises from a normal zero to levels seen in normal ovulatory cycles (5). This rise is evident after only a few days of therapy and is directly proportional to the dosage of estrogen administered. Moreover, if these women are given estrogen in the form of vaginal suppositories, the time lag between instigation of therapy and high cornification levels is dramatically lessened. This has been observed in our laboratories.

It is suggested that the variability in vaginal and cervical cornification counts may indicate either:

1. A greater sensitivity of the cervical epithelium to estrogen.
2. A difference in local concentrations of estrogen with a higher concentration in the cervix.
3. A combination of (1) and (2).

There are a number of observations which suggest that the cervix is particularly sensitive to estrogens. When müllerian tract carcinoma is produced in experimental animals by large doses of estrogens administered over a long period it is usually localized to the cervical tissue, suggesting that this tissue is the most highly reactive of all of the tissues of müllerian duct origin. Scannon described prenatal growth and natal involution of the human uterus and shows that after the 20th week in utero the uterus responds to the growth-stimulating effects of estrogens by enlarging. While

the body enlarges to only a limited extent, the cervix becomes twice as large in relation to the body of the uterus as it had been before. After birth, when presumably the estrogen stimulus is withdrawn, the cervix becomes relatively smaller in relation to the body of the uterus.

That the higher concentration of cornified cells in the cervix may be related to inflammation is suggested by the work of Brunelli (3). He re-

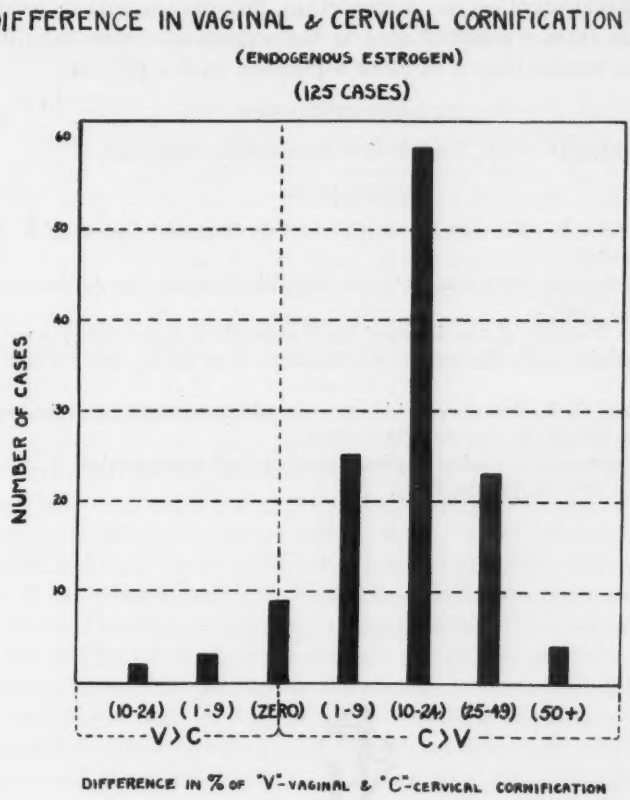

FIG. 1

ported the concentration and fixation of estrogen in inflamed tissues in rabbits.

The great frequency of chronic cervicitis in humans (80 per cent) arouses speculation as to whether there may be some etiological relationship between this disorder and the findings herein reported.

CONCLUSIONS

1. In a study of vaginal and cervical cytology smears on 125 female patients of all ages, a persistently higher cornification index was found in the cervical than in the vaginal smear. Factors which may be responsible for this variability are discussed.

2. If the cornification count is to be used as a quantitative index of the presence of endogenous estrogens in the human subject, a consistent technique for preparation of smears is important. Selective smears or scrapings with a spatula from a selected area of the vagina or cervix should give more accurate results than a random aspiration with a pipette.

ACKNOWLEDGMENT

We wish to thank Dr. G. N. Papanicolaou for discussing this paper.

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THE USE OF HYPERTONIC SALINE INFUSIONS IN THE DIFFERENTIAL DIAGNOSIS OF DIABETES INSIPIDUS AND PSYCHOGENIC POLYDIPSIA

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OBJECTIVE methods for differentiating polyuria and polydipsia of neurohypophysial origin from psychogenic polydipsia have hitherto been limited to prolonged urine concentration tests (2), a difficult procedure to carry out in many instances because of the attendant discomfort and lack of cooperation on the part of the patient.

Gilman and Goodman (4, 5) found that dehydration, as well as the oral administration of hypertonic saline, led to the appearance of an antidiuretic substance in the urine of normal, but not of hypophysectomized rats; an observation which has been confirmed in several other species of experimental animals (1, 7, 9, 11, 12, 14, 15, 16, 17).

Hare and his associates in a series of studies on normal dogs (8) have shown that the concentration of chlorides in the tubular reabsorbate (R) or the ratio of R to plasma chlorides (R/P) and the urine flow, are all decreased following infusions of hypertonic saline, concomitantly with an increase of antidiuretic substance in the urine. In hypophysectomized dogs, on the other hand, the procedure was associated with an elevation of chloride R/P, an increased urine flow and the absence of antidiuretic substance in the urine. These investigators (3) have also shown that these phenomena were due not to the sodium or chloride ion per se, but to a non-specific increase in the osmotic pressure of the plasma; the administration of hypertonic solutions of urea, sodium sulfate and sodium chloride to normal dogs was equally as effective in inducing the release of antidiuretic substance in the urine and the formation of a tubular reabsorbate with a lower osmotic pressure than that of the plasma. In 1944 (10) their studies were extended to man, their subjects consisting of one normal male and three patients with polyuria and polydipsia. On the basis of urine flow, the concentration of chloride in the tubular reabsorbate and the titer of antidiuretic substance in the urine during the administration of intravenous hypertonic

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saline, they were able to differentiate between psychogenic polyuria and polyuria due to neurohypophysial lesions.

Since this differentiation is so often difficult to achieve by other methods, it seemed desirable to investigate the reliability of this new diagnostic procedure by a study of a larger group of normal subjects and those with polyuria and polydipsia.

METHOD OF STUDY

Normal subjects and patients with polyuria and polydipsia were studied.[1] Their case histories are abstracted in the appendix. All antidiuretic therapy was stopped prior to the test for a period sufficient to permit the reappearance of polyuria and polydipsia, preferably to its original magnitude. Fluids were withheld for eight hours preceding the test but food was permitted. The subjects were hydrated with water, twenty cc. per kilogram by mouth, over a period of one hour. Thirty minutes after the period of hydration was begun, an indwelling catheter was inserted. Urine specimens were collected in fifteen minute periods and urine flow calculated in cc. per minute. After two control periods with an adequate urine flow, i.e., greater than five cc. per minute, an infusion of 2.5 per cent sodium chloride was begun. The hypertonic saline was administered intravenously at the rate of 0.25 cc. per kilogram per minute for forty-five minutes. If no decrease in urine flow occurred during the infusion or in the first two post-infusion periods (15 minutes each), 0.1 unit of pitressin (Parke-Davis) was given intravenously and its effect on urine flow observed.

RESULTS

Nine healthy young adults, 8 males and 1 female, showed a prompt and marked decrease in urine flow during the infusion or the first period thereafter (Table 1 and Fig. 1), the flow being reduced to 7–26 per cent of the maximum during the pre-infusion periods. In 3 instances the maximal urine flow occurred during the first 15-minute period of the infusion. That the reduction of urine flow was not due to saline per se was evident from the failure of isotonic saline infusions to inhibit urine flow (Fig. 2). The reduction of urine flow was not of spontaneous origin, diuresis continuing after hydration alone for periods up to one and a half hours, the usual duration of the test (Fig. 2). In 2 of 3 normal subjects, the decreased urine flow during the infusion could be abolished (Fig. 2) or delayed (Fig. 1, subject T. C.) by previous overhydration or the continued ingestion of water during the infusion.

[1] We are indebted to Dr. Henry Barnett of the Department of Pediatrics, Cornell University Medical College, for permission to include his results in two cases (*L. G. and N. B.*) studied on the Pediatrics Service.

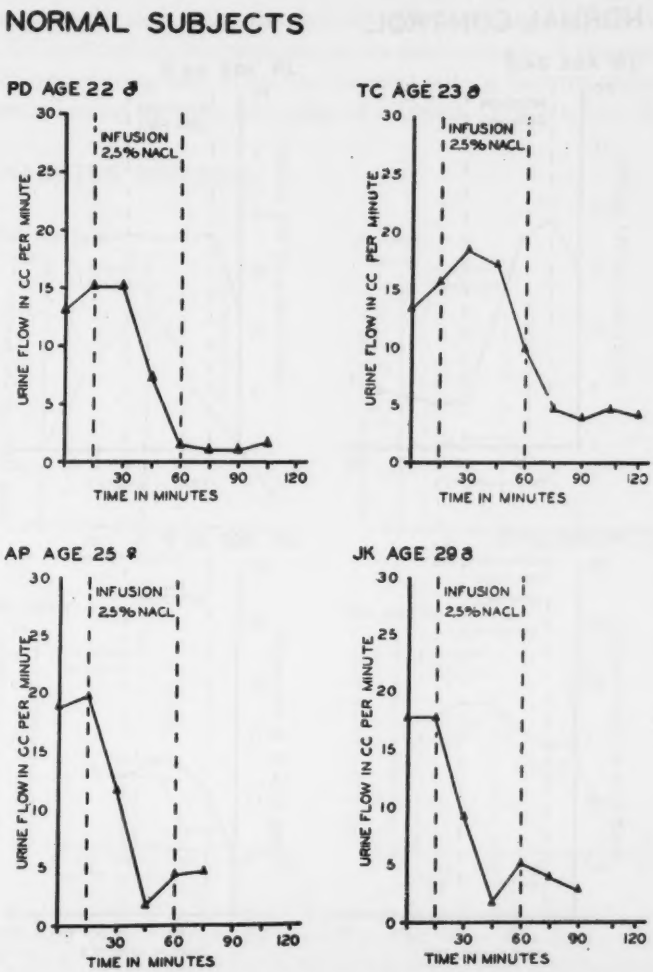

FIG. 1. Response of 4 representative normal subjects to infusion of 2.5 per cent NaCl (0.25 cc/kg/min. for 45 minutes) following previous hydration. Subject *T.C.*, maximal urine flow occurred during the first 15-minute period of the infusion and there was a slight delay in the antidiuretic response which was, however, maximal in the first post-infusion period (see text).

Investigations were made on the possible influence of renal disease on the reliability of this test procedure. Two patients with moderate renal insufficiency, one with renal calculi, the other with renal calcinosis, and one patient with renal calculi and minimal renal damage, all showed a prompt

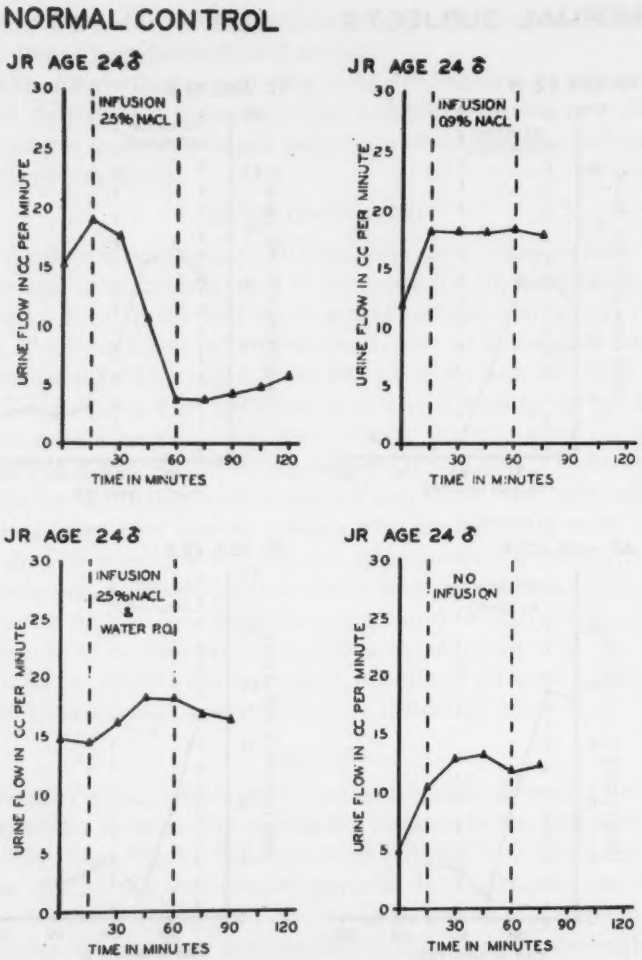
NORMAL CONTROL
JR AGE 24 ♂
INFUSION 25% NACL
URINE FLOW IN CC PER MINUTE
TIME IN MINUTES
JR AGE 24 ♂
INFUSION 0.9% NACL
URINE FLOW IN CC PER MINUTE
TIME IN MINUTES
JR AGE 24 ♂
INFUSION 25% NACL & WATER P.O.
URINE FLOW IN CC PER MINUTE
TIME IN MINUTES
JR AGE 24 ♂
NO INFUSION
URINE FLOW IN CC PER MINUTE
TIME IN MINUTES

FIG. 2. Illustrates characteristic antidiuretic response of normal subject to hypertonic NaCl infusion (upper left) and failure of isotonic NaCl infusion to induce antidiuresis (upper right). Lower left graph illustrates the abolition of antidiuresis by continued oral hydration during the infusion of hypertonic saline. Lower right graph shows the sustained diuresis following hydration in the absence of a hypertonic saline infusion (see text).

reduction in urine flow comparable to the normal subjects during the infusion of hypertonic saline (Table 1). In 3 patients with severe renal insufficiency the urine flow during the period of hydration was so low the test could not be carried out.

Eleven patients with polyuria and polydipsia without glycosuria were studied. In contrast to the response of normal subjects, 8 showed a continued diuresis during and after the infusion with a prompt reduction of urine flow following the administration of pitressin (Table 1, Fig. 3). These

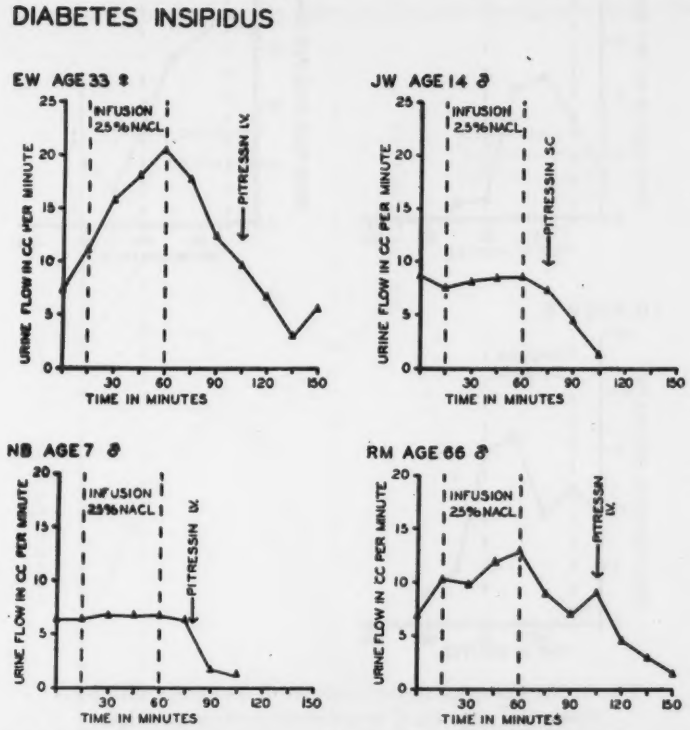

FIG. 3. Four representative responses of patients with diabetes insipidus of neurohypophysial origin. Note continued diuresis and prompt response to intravenous pitressin. In *E.W.* the reduction of urine flow in the post-infusion period prior to pitressin was only 13.6 per cent below the pre-infusion maximum.

results provided objective support to the clinical impression that these patients had diabetes insipidus due to insufficiency of the neurohypophysis.

Three of the subjects with polyuria and polydipsia showed the marked decrease in urine flow characteristic of the normal subject, during or immediately after the infusion of hypertonic saline (Fig. 4). The psychogenic origin of their polydipsia and polyuria was confirmed by their subsequent freedom from symptoms without replacement therapy.

A comparison of representative responses of a normal subject and of

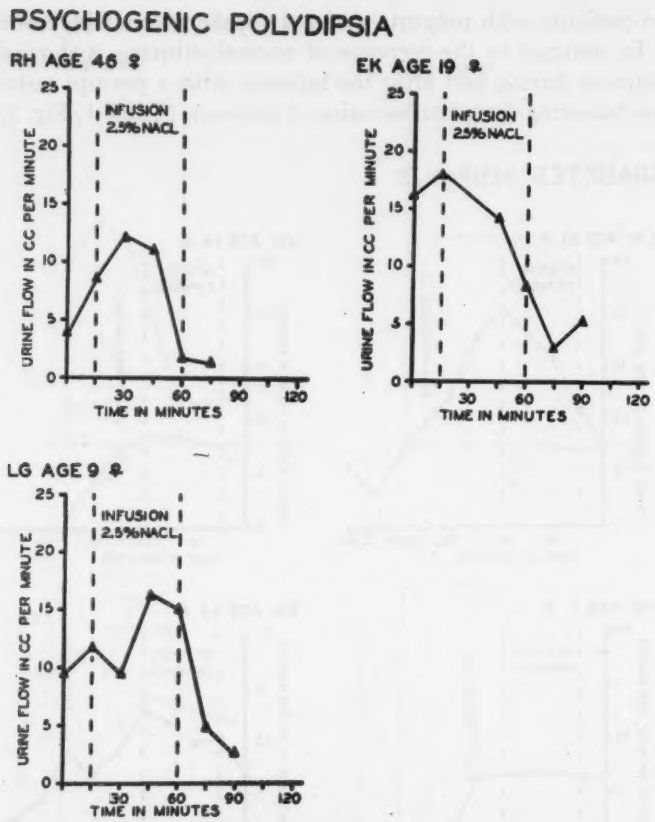

FIG. 4. Normal antidiuretic responses of 3 subjects with polydipsia and polyuria of established psychogenic origin.

patients with psychogenic and neurohypophysial polyuria and polydipsia is provided in Fig. 5.

Three subjects with well controlled diabetes mellitus and mild glycosuria were also studied (Table 1). One, without polyuria, showed the normal decrease in urine flow during the infusion. The other two had an associated polyuria and polydipsia; one exhibited a normal decrease in urine flow, the other a continued diuresis during and after the infusion.

DISCUSSION

These experimental results, in conjunction with the experience of Hare and his associates in dogs and man, indicate that the response of hydrated

subjects to hypertonic saline infusions provides a simple, objective means of differentiating between polyuria and polydipsia of neurohypophysial and psychogenic origin. The test is simple; it requires no special equipment, may be performed on the ambulatory patient, and is completed within three hours. Care should be taken to avoid overhydration, since the essence of the procedure consists in the release of antidiuretic substance from the

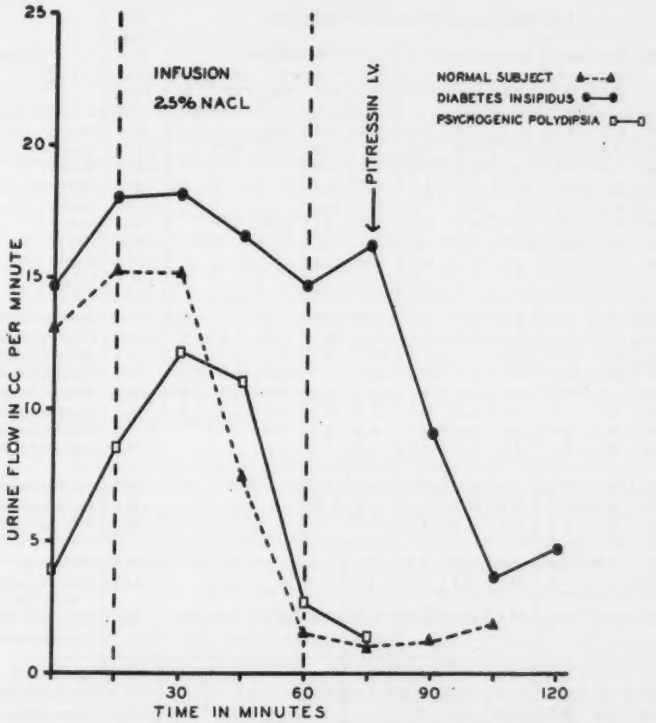

FIG. 5. Comparison of representative responses to hypertonic NaCl of the normal subject and patients with neurohypophysial and psychogenic polyuria and polydipsia.

posterior pituitary in response to the increased osmotic pressure of the blood resulting from the hypertonic infusions. The site of action is placed by Hare (6) in the diencephalon, by others (13, 14, 15) in the osmoreceptors of the carotid.

Whether or not this procedure, in which urine flow is the only index used, will prove capable of differentiating polyuria of neurohypophysial origin when there is an associated glycosuria or renal disease requires further investigation. In the presence of renal disease the absence of an antidiuretic

effect might be due to the inability of the tubules to respond to the posterior pituitary stimulus. Under these circumstances the tubules should also fail to respond to the administration of pitressin, thereby permitting a localization of the defect to the renal tubules. Other complications which may interfere with the interpretation of the test are those associated with

TABLE 1

Subject	Age	Sex	Urine Flow in cc. per Minute per 15 Minute Period										% Change in Urine Flow†	Diagnosis
			Preinfusion		Infusion 2.5% NaCl			Post-infusion						
			I	II	III	IV	V	VI	VII	VIII	IX	X		
P.D.	22	M	13.0	15.2	15.1	7.3	1.5	1.0	1.2	1.8			−93.5	Normal
T.C.	23	M	13.2	15.6	18.5	17.2	9.9	4.7	3.8*	4.7*	4.0*		−77.0	Normal
D.H.	22	M	6.8	10.7	12.0	9.0	1.5	5.1	3.0				−86.0	Normal
K.H.	39	M	10.7	16.0	16.4	7.7	1.7	2.7	2.4				−89.5	Normal
C.R.	27	M	20.0	21.5	29.7	20.7	7.9	5.6	11.3				−74.0	Normal
J.R.	24	M	15.3	19.3	17.6	10.8	3.9	3.6	4.4	4.8*	5.8*		−76.5	Normal
K.B.	23	M	24.9	28.3	27.7	7.7	2.3	2.4	2.0				−93.0	Normal
J.K.	29	M	17.7	17.7	9.1	1.7	5.1	3.9	2.6				−90.5	Normal
A.P.	25	F	18.7	19.7	11.7	1.7	4.3	4.7					−91.5	Normal
S.S.	15	F	8.0	7.3	8.0	12.3	9.8	4.0	2.3				+18.6	Diabetes Insipidus
T.K.	45	M	15.3	16.6	20.0	20.0	18.6	18.6	16.6	8.0	1.0		+21.2	Diabetes Insipidus
M.P.	38	M	14.6	18.0	18.2	16.5	14.8	16.2	9.1	3.6	4.7		−17.8	Diabetes Insipidus
M.F.	13	F	15.3	15.0	15.7	16.3	15.7	14.7	11.7	10.0*	10.0	2.5*	−33.3	Diabetes Insipidus
R.M.	66	M	7.0	10.3	9.7	11.7	12.7	9.0	7.0	9.0*	4.5*	3.0*	−32.0	Diabetes Insipidus
E.W.	33	F	7.3	11.0	15.7	18.0	20.0	17.7	12.3	9.5	6.5	3.0	−13.6	Diabetes Insipidus
N.B.	7	M	6.3	6.3	6.7	6.6	6.7	6.2	1.6	1.0			− 0.2	Diabetes Insipidus
J.W.	14	M	8.6	7.5	8.0	8.3	8.3	7.3	4.3*	1.2*			−15.1	Diabetes Insipidus
E.K.	19	F	16.0	18.0		14.0	8.3	3.0	5.3				−83.5	Psychogenic polydipsia
L.G.	9	F	9.46	11.7	9.34	16.34	15.0	4.73	2.53				−78.5	Psychogenic polydipsia
R.H.	46	F	3.8	8.5	12.1	11.0	2.6	1.3					−80.5	Psychogenic polydipsia
M.B.	27	F	11.0	16.0	18.0	15.7	4.3	6.0	3.5				−78.0	Diabetes mellitus
R.B.	13	M	11.3	13.7	17.7	4.7	5.7	6.0	5.0				−65.0	Diabetes mellitus with polyuria and polydipsia
F.R.	19	M	12.7	13.3	17.3	13.7	11.0	9.0	10.3	12.3	1.7	3.3*	−32.4	Diabetes mellitus with polyuria and polydipsia
G.P.	39	M	11.6	15.5	11.1	6.3	3.0	5.6					−80.5	Renal calculi
B.K.	27	F	7.3	16.6	14.3	5.13	3.93	4.9					−76.5	Renal calcinosis
F.C.	35	M	9.7	10.0	10.6	1.8	0.7						−93.0	Renal calculi

* Indicates ten-minute period.

† Maximal per cent change in urine flow as compared with maximal urine flow prior to hypertonic infusion and without pitressin. Figures in bold face indicate urine flow in cc./minute after 0.1 U pitressin.

marked decreases or increases in the extracellular fluid volume, such as edema or extreme dehydration.

This procedure may prove useful in determining whether alterations in neurohypophysial function may be involved in the antidiuretic phenomena observed in a number of conditions such as cardiac decompensation, hepatic cirrhosis and premenstrual edema. This possibility is now being explored, utilizing, in addition to urine flow, the measurement of the chloride and osmotic R/P.

CONCLUSIONS

Evidence has been presented, derived from a study of normal subjects and patients with polyuria of both neurohypophysial and psychogenic origin, that alterations of urine flow of hydrated subjects, following hypertonic saline infusions, permit a differentiation between diabetes insipidus and psychogenic polydipsia and polyuria.

APPENDIX

Case Histories

Case 1. S.S. (*N.Y.H. 419,783*). A 15-year old white school girl complained of polyuria and polydipsia of 3 years' duration. The patient had found complete relief of nocturia by taking dried posterior pituitary intranasally before retiring. Breast development, axillary and pubic hair appeared at 14 but menstruation had not begun. Physical Examination: The blood pressure was 114/72, mm. Hg. Axillary and pubic hair was scant, and the breasts were poorly developed. Laboratory Data: The blood count, urine analysis, blood chemistry, glucose tolerance test, spinal fluid analysis and visual fields were all within normal limits. Roentgen-rays of the long bones and skull were negative. The basal metabolic rate was minus 13 per cent. The concentration of 17-ketosteroids was 13.0 mg. per 24 hours. Vaginal smears showed acyclic ovarian insufficiency. The fluid intake was from 5,000 to 7,200 cc. The urine output was from 6,000 to 8,200 cc., per 24 hours, the maximal specific gravity on a prolonged concentration test being 1.006. The patient has since been well regulated by the administration of dried posterior pituitary powder by nasal insufflation three times a day.

Case 2. T. K. (*N.Y.H. 398,498*). A 45-year old white married butcher had had polyuria and polydipsia of long duration. Twelve years previously the patient first noticed nocturia, followed by polyuria and polydipsia of "several gallons a day." Shortly after the onset of symptoms, there was a marked loss of scalp hair. Polyuria and polydipsia were controlled by 10 units of pitressin subcutaneously twice a day until 2 months prior to admission, when 20 units twice a day failed to control the polyuria and polydipsia. The patient had been married 10 years and had no children. Physical Examination: The blood pressure was 150/105 mm. Hg. Generalized obesity was evident. Laboratory Data: The urine showed a faint trace of albumin, occasional RBC and from 4 to 5 WBC per high power field. The blood chemistry, glucose tolerance test and spinal fluid analysis were within normal limits. The skull roentgen-ray was negative. Maximal urine specific gravity on a standard urine concentration test was 1.005. The basal metabolic rate was plus 13 per cent. The 17-ketosteroids measured 7.6 mg. per 24 hours. Semen analysis showed a subnormal count with very poor motility. The patient has since been well regulated by the administration of dried posterior pituitary powder by nasal insufflation three times a day.

Case 3. M.P. (*N.Y.H. 334,107*). A 38-year old white, single male had suffered from polyuria and polydipsia since the age of 20. Headaches had been present since childhood as well as frequent upper respiratory infections. The patient had undergone two submucous resections and two tonsillectomies and at the age of 21, an enucleation for ophthalmitis. During the 6 years preceding his illness, he had sustained several severe blows to the head, without loss of consciousness. Physical Examination: The blood pressure was 130/80 mm. Hg. Generalized obesity was evident. He had bilateral chronic otitis

media and an artificial right eye. Laboratory Data: The urine analysis, blood count and blood chemistry were within normal limits. Roentgen-rays of skull and chest were negative. The left visual field was normal. Sinus roentgen-rays showed left ethmoidal and maxillary sinusitis. The fluid intake was from 4,000 to 13,500 cc.; urine output was from 4,050 to 10,250 cc. per 24 hours with a maximal urine concentration of 1.007. The patient has been controlled by the administration of dried posterior pituitary powder, intranasally, and pitressin tannate in oil; however, because of unpleasant reactions to all pituitary preparations, he rarely takes any antidiuretic therapy.

Case 4. M.F. (*N.Y.H. 407,007*). An 11-year old white school girl had had polyuria and polydipsia for 3½ months. Four months before the onset of her illness she had a fall from a bicycle, which was followed by dizziness, unilateral weakness and vomiting for several days. Spinal fluid and skull roentgen-rays at another hospital were said to be negative. The menarche occurred one month after the onset of illness. Physical Examination: The blood pressure was 104/80 mm. Hg. Moderate acne was present. The patient showed well developed secondary sexual characteristics. Laboratory Data: The blood count, blood chemistry, spinal fluid analysis and urine examination were within normal limits. Roentgen-ray of the skull was negative and the visual fields were normal. The electro-encephalogram was suggestive of defect in the frontal lobes, but equivocal. The fluid intake was from 6,300 to 12,800 cc. and the urine output from 4,475 to 11,800 cc. per 24 hours with a maximal specific gravity of 1.007. The patient was poorly regulated with pitressin, subcutaneously, and by nasal spray, but has subsequently been well controlled with dried posterior pituitary powder by nasal insufflation three times a day.

Case 5. R.M. (*N.Y.H. 404,769*). A 64-year old white, married salesman had had polyuria and polydipsia of three years duration which had been controlled with pitressin therapy. Six years previously the patient acquired syphilis and received treatment with arsenic and bismuth. The Wassermann test was negative 3 years ago. Physical Examination: Blood pressure was 160/100 mm. Hg. The fundi showed macular degeneration and hemorrhages. The heart was not enlarged and no murmurs could be detected but the peripheral vessels were sclerotic. Laboratory Data: The blood count, urine analysis, blood chemistry, skull roentgen-ray, electro-encephalogram and visual fields were within normal limits. The blood Wassermann test was equivocal and the spinal fluid Wassermann, 2+ at 0.6 dilution. Roentgen-ray of the chest showed pulmonary tuberculosis, apparently healed; gastric washings showed Gaffkey 1. The fluid intake was from 2,400 to 16,000 cc. and the urine output from 4,800 to 15,700 cc. per 24 hours with a maximal specific gravity of 1.009. The patient has since been well regulated with dried posterior pituitary powder by nasal insufflation, three times daily.

Case 6. E.W. (*N.Y.H. 313,960*). A 33-year old white, single female had suffered from polyuria and polydipsia since childhood. Breast development began at 16, sex hair appeared at 16, but the patient had never menstruated spontaneously. She had poliomyelitis at 2½ years, with residual weakness of left leg. She suffered from frequent headaches of considerable severity. Physical Examination: The blood pressure was 106/70 mm. Hg. The patient was a short female with generalized obesity, atrophic skin and scant body hair. Her breasts contained little glandular tissue. There was moderate atrophy of the left leg with shortening, and absent knee and ankle jerks. Laboratory Data: The urine analysis, blood count, and blood chemistry were within normal limits. Roentgen-rays of the skull were negative, but those of the long bones, revealed moderate osteoporosis. A biopsy showed atrophy of the skin. Smears showed vaginal atrophy. The fluid intake

was from 2,700 to 4,400 cc. and the urine output from 2,900 to 4,800 cc. per 24 hours with maximal specific gravity on a prolonged concentration test, 1.016. The 17-ketosteroid excretion was 10.0 mg. per 24 hours.

Case 7. N.B. (*N.Y.H. 464,203*). A 7½-year old, white schoolboy had had polyuria and polydipsia since the age of 4. Bilateral otitis media had been present since the age of 9 months and had been treated with roentgen-ray, radium and two right mastoidectomies with a resultant right facial paralysis. Physical Examination: The blood pressure was 110/70 mm. Hg. There was a purulent discharge from the right ear and deafness. The right cervical lymph nodes were enlarged. Laboratory Data: The urine analysis, blood count, blood chemistry and spinal fluid analysis were within normal limits. Roentgen-rays of skull and chest were negative. Visual fields were negative. A smear of a cervical lymph node was positive for tubercle bacilli. The fluid intake was 4,660 cc. and the urine output 4,535 cc. per 24 hours, with maximal specific gravity of 1.001. The patient has since been regulated by the administration of 0.75 cc. pitressin tannate in oil twice daily.

Case 8. J.W. (*N.Y.H. 360,161*). A 14-year old, white schoolboy with polyuria and polydipsia since the age of 5 was made available for these studies through the kindness of Dr. Bronson S. Ray. At the age of 10, the patient had a right temporal hemianopsia, vision on the left being limited to light perception. At this time Dr. Ray partially resected a malignant chromophobe struma of the pituitary. This was further treated by two courses of irradiation. Polyuria and polydipsia persisted. During the previous year the patient had grown 13 cm. and gained 13 kg. Physical Examination: The blood pressure was 110/80 mm. Hg. The patient was an obese boy with fat pads over the hips and breasts, no sex hair and prepuberal genitalia. Laboratory Data: The blood count, urine analysis and blood chemistry were within normal limits. The 17-ketosteroid excretion was 3.03 mg. per 24 hours. Visual fields and roentgen-ray of the skull were within normal limits. The fluid intake was from 3,000 to 4,000 cc., and the urine output from 5,000 to 6,000 cc. per 24 hours, with a maximal specific gravity 1.005. The patient has since been regulated by the administration of dried posterior pituitary powder by nasal insufflation from 3 to 4 times daily.

Case 9. E.K. (*N.Y.H. 455,825*). A 19-year old white, female secretary had polyuria and polydipsia for from 5 to 6 years. She drank from 15 to 20 glasses of fluid a day and voided about 15 times during the day and night. The menarche occurred at the age of 13, with an excessive growth of facial hair starting at that time. Physical Examination: The blood pressure was 130/85 mm. Hg. Slight hypertrichosis was evident but the clitoris was not enlarged. Laboratory Data: The blood count and urine analysis were within normal limits. Roentgen-ray of the skull was negative. The basal metabolic rate was −9 per cent. Vaginal smears revealed an anovulatory cycle with low follicular activity. The 17-ketosteroid excretion was 10.8 mg. per 24 hours. Maximal urine specific gravity was 1.019. Since the performance of the hypertonic saline test, the fluid intake has been voluntarily reduced to 7 glasses of fluid a day without discomfort and there has been no frequency.

Case 10. L.G. (*N.Y.H. 424,561*). A 9-year old white schoolgirl had suffered from polyuria and polydipsia for 1 year and from excessive weight gain for 2 years. The fluid intake was "3 to 4 quarts a day" and frequency 14 times a day. Physical Examination: The blood pressure was 110/70 mm. Hg. The patient showed generalized obesity. Laboratory Data: The urine analysis, blood count and blood chemistry were within normal limits.

Roentgen-rays of skull and long bones were negative. The maximal urine specific gravity on a concentration test was 1,039. The patient's polyuria and polydipsia are no longer present.

Case 11. R.H. (*N.Y.H. 466,849*). A 46-year old white, registered nurse showed polyuria, polydipsia and weight gain of 3 months' duration. The fluid intake was from 3,400 to 7,500 cc., and the urine output 5,600 cc. per 24 hours. She had had menopausal symptoms for 4 years following a panhysterectomy, only partially controlled with Progynon D. H. 0.1 mg. per day. Thirty-nine years ago the patient had had "brain fever" characterized by drowsiness and fever for 9 months. Physical Examination: The blood pressure was 140/90 mm. Hg. Laboratory Data: The blood count and urine examination were essentially negative. The skull roentgen-ray was negative. Maximal urine concentration was 1.006. Since the performance of the hypertonic saline test and adequate estrogen replacement therapy, the patient has had no polyuria and polydipsia.

Case 12. M.B. (*N.Y.H. 402,056*). A 27-year old, white, married housewife with known diabetes mellitus for 3 years, was regulated with 50 units protamine zinc insulin and 50 units regular insulin daily. She had no polyuria or polydipsia. Her weight was constant. Physical Examination: Except for a diffusely enlarged thyroid there were no important findings. Laboratory Data: Urine analysis showed sugar 2+, acetone 0, and specific gravity 1.018. The blood count was within normal limits.

Case 13. R.B. (*N.Y.H. 34,863*). A 13-year old, white schoolboy entered the hospital in diabetic acidosis. After the diabetes mellitus was controlled with insulin, the patient continued to have polyuria and polydipsia. Physical Examination: Essentially negative, B.P. 120/70 mm. Hg. Laboratory Data: The urine showed sugar 1+ and specific gravity 1.014. The blood count and roentgen-ray of the skull were normal. The fluid intake was from 800 to 3,200 cc. and the urine output from 1,200 to 7,000 cc. per 24 hours. The papatient has since been regulated with 45 units protamine zinc insulin, has only occasional polyuria and polydipsia, and has maintained constant weight.

Case 14. F.R. (*N.Y.H. 36,589*). A 16-year old, schoolboy had a long history of polyuria and polydipsia, loss of vision, drowsiness and frontal headaches. At the age of 13 he was obese, underdeveloped and had no secondary sexual characteristics; the fundi revealed pallor of the optic discs and bilateral macular degeneration. The patient was treated with chorionic gonadotropic hormone and methyl testosterone, with resulting development of secondary sexual characteristics. Laboratory studies and roentgen rays were negative at this time. Three years later, the patient was admitted to the hospital in diabetic acidosis. Physical Examination: The blood pressure was 114/74 mm. Hg. The fundi showed macular degeneration. The patient had the typical eunuchoid body habitus. Laboratory Data: The urine showed sugar 4+, specific gravity 1.026. The blood count was within normal limits. Roentgen-ray of the skull was negative. Examination of the visual fields revealed bilateral, bitemporal scotomata not considered due to pituitary enlargement. The fluid intake was from 3,100 to 5,100 cc. and the urine output from 2,360 to 5,050 cc. per 24 hours. The diabetes mellitus has since been controlled with 25 units protamine zinc insulin daily; however, polyuria and polydipsia have continued, but without weight loss.

Case 15. G.P. (*N.Y.H. 445,407*). A 39-year old white, male clerical worker had suffered from known renal calculi for five years. He had frequency every 2 hours, nocturia

0–3, intermittent dysuria and flank pain. Physical examination was essentially negative. The blood pressure was 120/88 mm. Hg. Laboratory Data: The urine and blood count were within normal limits. Serum calcium was 12.16 mg. per cent; phosphorus, 1.69 mg. per cent and alkaline phosphatase 3.7 Bodansky units. Urinary calcium was 350 mg./24 hours on a 130 mg. calcium diet. The maximal urine concentration was 1.021. Roentgen-ray of the skeletal system showed hypertrophic osteoarthritis of the cervical and dorsal spine and aseptic necrosis of the left scaphoid. Intravenous pyelograms revealed right renal calculi and a left renal calculus. Two normal parathyroids were removed with subsequent lowering of the serum and urinary calcium and a rise of the serum phosphorus.

Case 16. B.K. (N.Y.H. 426,251). A 27-year old white, married housewife had had a parathyroidectomy one year previously with removal of a parathyroid adenoma from the anterior mediastinum, for hyperparathyroidism associated with marked bone lesions and renal calcinosis. Physical examination was essentially negative. The blood pressure was 136/86 mm. Hg. Laboratory Data: The blood count, urine analysis and blood chemistry were within normal limits. The urea clearance was 53.3 per cent, and phenol sulfonphthalein test 83 per cent. The fluid intake was from 1,200 to 2,150 cc. and the urine output from 1,070 to 2,000 cc. per 24 hours with a maximal specific gravity of 1.016. Roentgen-ray of the skeleton showed healing osteitis fibrosa cystica.

Case 17. (N.Y.H. 461,452). A 35-year old Puerto Rican mechanic with a 10-year history of renal calculi recently had a transurethral resection with removal of vesicle calculi and a left nephrolithotomy. Physical Examination was essentially negative. The blood pressure was 120/80 mm. Hg. Laboratory Data: The urine showed a faint trace of albumin and many clumps of WBC. A count showed 100 WBC and 0–10 RBC per high power field. The blood count and blood chemistry were within normal limits. The maximal urine concentration was 1.012, and the phenolsulfonphthalein test showed a clearance of 78 per cent. A urine culture revealed Aerobacter aerogenes. Intravenous pyelograms showed fair bilateral renal function with calyceal deformity indicating old pyelonephritis.

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THIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM COMPLICATING PREGNANCY AND ITS EFFECT ON THE HUMAN FETAL THYROID

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THIOURACIL has been in use for the past 4 years. Astwood (1) has reported its use in four pregnant patients without untoward results. Palmer (15) treated 3 pregnant women, one of whom delivered a normal child. Eaton (4) has reported 2 cases in which thiouracil was used. One of these was the only case in which the child's thyroid was enlarged at delivery and remained so for several months after birth, but the child was otherwise normal. Vogt (17) treated one pregnant patient with thiouracil; although she herself developed a marked enlargement of the thyroid, the child was normal.

Only a few experimental papers have been published, including that of Goldsmith et al. (7) who recorded that newborn rats whose mothers had been treated daily with thiourea were both normal in weight and in external appearance as compared with the controls. He noted that the thyroid was slightly increased in weight and there was active hyperplasia characterized by high columnar epithelium with a limited amount of stainable colloid. These effects disappeared when the animals were placed on a laboratory stock diet.

The use of any drug during gestation always raises the question of possible toxicity of the medication for the fetus. This is especially true in regard to the thyroid. Williams (20) has demonstrated that thiouracil does pass through the placenta in rats. Hughes (9) has shown that by repeated doses of thiouracil to newborn rats it is possible to induce cretinism in these animals. This was confirmed by Freiesleben and Kjerulf-Jensen (6). The thyroid gland of these animals increased in weight and showed typical hyperplastic changes and a decrease in the colloid contents.

The time of the administration of this drug during pregnancy necessitates a knowledge of the embryonic development of the thyroid. It is not before the fifth month that follicular-like structures are present in the fetus. Colloid has been demonstrated in approximately the sixth month. The first evidences of secretion into the individual follicles are noted at

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the seventh month of intrauterine life. The gland, however, has numerous solid cell nests even at birth. Grollman (8) believes it is probable that the thyroid is functional in early embryonic life and that its dysfunction at this stage, as for example in cretins, may result in abnormality of the fetus. Means (13) states that the thyroid is probably fully functioning at birth. Zondek (23) supports this theory by citing the case of a myxedematous female whose condition markedly improved during her pregnancy. Windle (21) noted that human infants born with or without atrophic thyroids exhibit none of the symptoms of cretinism; however, a latent athyreosis soon manifests itself. It seems probable to him that, in humans, the

TABLE 1. INCIDENCE OF HYPERTHYROIDISM IN PREGNANCY

Author	Year	Region	Series of Pregnancies	Cases of Hyperthyroidism	Percentage Incidence
Markoe (12)	1918	New York	100,000	8	0.008
Yoakum (22)	1928	Michigan	937	35	3.7
Wallace (18)	1933	New York	11,571	9	0.07
Portis & Roth (16)	1939	Illinois	1,000	14	1.4
Javert (10)	1940	New York	23,439	18	0.076
McLaughlin & McGoogan (11)	1942	Nebraska	6,112	19	0.3
Whitelaw	1947	New York	13,264	8	0.06
TOTAL			156,323	111	0.071

mother's hormone is available to the fetus because it can transverse the placental barrier. The transversal of thyroglobulin is denied by others and this opposing theory is substantiated by the studies of Dorff (3) on two sets of twins in which one twin in each set was a sporadic cretin. Faxen (5) reported similar findings the following year. It is known, of course, that the onset of sporadic cretinism is insidious, and that the symptoms are usually not recognizable before the third month. Therefore, it is of the utmost importance that we know whether thiouracil or any of its derivatives could induce cretinism in the human.

Fortunately, toxic hyperthyroidism is an uncommon complication of pregnancy. The incidence of hyperthyroidism complicating pregnancy for the period 1935–45 at Binghampton City Hospital and Charles S. Wilson Memorial Hospital was 0.06 per cent. The opportunities, therefore, for evaluating any drug in the treatment of hyperthyroidism complicating pregnancy are very limited for the individual worker. The author has treated 3 pregnant hyperthyroid women with thiouracil. One aborted at

3 months, although her basal metabolism was normal; the second delivered at term a normal baby whose thyroid showed no enlargement; and the third case, because it is so unusual, is presented below:

CASE REPORT

G.D. a 30-year old white female, para I, gravida II, in the 26th week of pregnancy was first admitted to the hospital on September 24, 1944 complaining of dizziness and nausea. These symptoms had first been noted approximately two years previously, together with loss of weight and mild exophthalmos, and had become markedly aggravated during the second month of this pregnancy. The patient had first noticed her goiter ten years previously, but had experienced no toxic symptoms up to two years ago. During and after her first pregnancy, five years previously, she had noticed an increase in the

TABLE 2. *Case G.D.*

	On Admission	1 Week before Delivery
Basal metabolic rate	+65 per cent	+8 per cent
Circulation time	8 sec.	14 sec.
Creatine excretion	420 mg./24 hrs.	160 mg./24 hrs.
Blood Cholesterol	105 mg./100 cc.	240 mg./100 cc.

size of her goiter. This gestation had been uneventful, however. Up to one week prior to her hospital admission the patient had not seen a physician.

Physical examination revealed a thin, markedly nervous, white female with moderate exophthalmos. Positive findings were a lid lag, a smooth and moderately enlarged thyroid, a resting pulse rate of 140 and a blood pressure 150/90 mm. Hg. The skin was moist and warm, there was a generalized increase in the reflexes and there was a fine tremor of the hands. The uterus corresponded in size to the period of amenorrhea. The fetal heart sounds were normal. Her basal metabolic rate on admission was +65 per cent. The creatine excretion was 420 mg. per 24 hours. Circulation time was 8 seconds. The patient was given general supportive treatment which included large doses of Vitamin B complex, a high-vitamin, high-caloric diet, and was given 0.6 grams daily of thiouracil[1] for one week, after which the dosage was reduced to 0.4 grams a day. During her stay in the hospital bi-weekly check-ups of her white blood count and differential failed to reveal any significant changes. Her condition rapidly improved and her basal metabolic rate, pulse and blood chemistry, as well as circulation time were within normal range at the time of delivery (Table 2). Parturition was uneventful. The baby was an anencephalic male monster[2] with a cleft palate born the 41st week of pregnancy. Its weight was 2736 grams. It lived six hours. Permission was granted for removal of the thyroid only, which was dissected out 10 minutes after death. The wet, fresh gland weighed .828 grams. It was then fixed for an analysis of its iodine content and for microscopic study (Figs. 1 & 2). The iodine values of two different sections were 5.58 and 5.59 mg. of iodine per 100 grams

[1] I wish to thank Dr. Hardy for the thiouracil used in this study.

[2] Dean (2) has reported a relationship of two cases of anencephalic monstrosities born to the same woman suffering from hyperthyroidism.

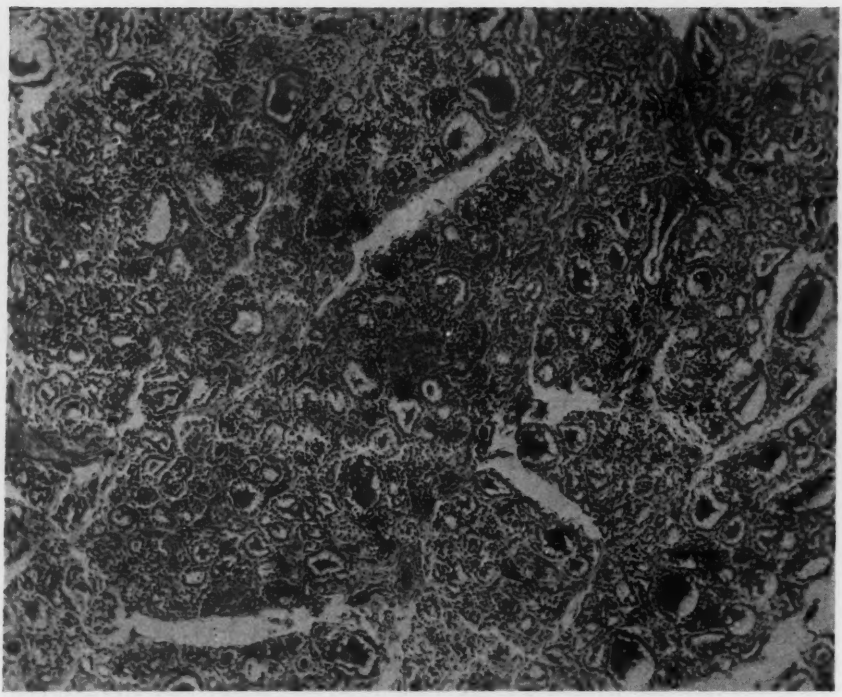

FIG. 1. Photomicrograph of a section of thyroid of a newborn from a mother with hyperthyroidism (*Case G.D.*) (× 150)

of wet tissue. This is well within the range of iodine values for the thyroid of the normal newborn. Histological sections of the gland revealed little change from that found in the thyroid of a corresponding newborn infant.

DISCUSSION

In this markedly toxic hyperthyroid pregnant female, thiouracil, used over a period of three months, brought the basal metabolic rate down to normal and maintained it. This is in contrast to iodine medication, where it has been pointed out by Means and Lerman (14) that the lowest value reached is still above the normal range. Wieland (19) has reported in his study on weights of newborn thyroid that they all exceed 1 gram. Nearly all authors, both in this country and abroad, are agreed that the normal gland of the newborn weighs approximately one gram or slightly more in the wet, fresh state. Therefore, it can be seen that there was no increase in the weight of this specimen over the average normal. In fact it was some-

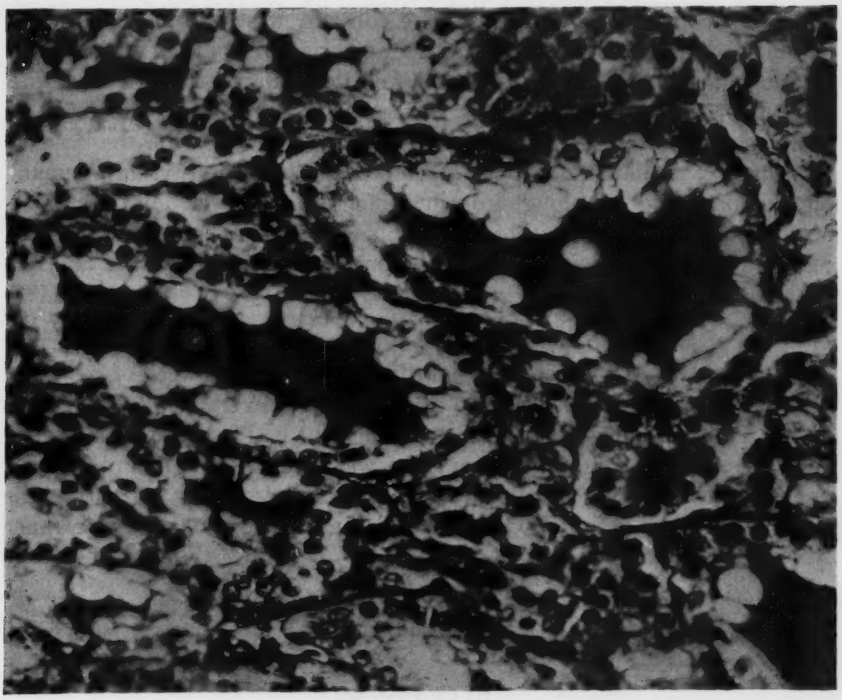

FIG. 2. Same as Figure 1. (× 770)

TABLE 3. THYROID WEIGHTS OF NEWBORN

City or Country	Wet Weight
	gm.
Kiel (Wegelin)	1.9
Königsburg (Wegelin)	3.5
Berlin (Kloeppel)	5.7
Freiburg (Kloeppel)	10.7
Munich (Wegelin)	6.0
Austria (Guggisberg)	1–2
Switzerland (Wegelin)	8.2
Finland (Leidenius)	3.2
Holland	1½–3
Author's case	0.828

what below average. The total iodine content, which included both inorganic and organic iodine, also showed no variation from the normal. The histologic appearance of the tissue showed that the gland had a moderate amount of colloid and gave little indication of having been subjected to prolonged thiouracil medication (Fig. 2). It would appear on the basis of this single case that thiouracil administered to the hyperthyroid pregnant female does not exert enough injurious effect on the thyroid of the human newborn to be detected either microscopically or chemically. This agrees with the experimental findings in rats reported by Freiesleben and Kjerulf-Jensen (6).

SUMMARY

A markedly hyperthyroid pregnant female in the 26th week of gestation was treated with thiouracil up to and through delivery. She received 0.6 grams per day for one week, following which she had 0.4 grams per day for 13 weeks. At the time of delivery she was free of toxic symptoms. An anencephalic monster was delivered whose thyroid gland fell within the normal range in weight, iodine content, and in histological appearance when it was examined.

ACKNOWLEDGMENT

I wish to thank Dr. Astwood for the iodine determinations and Dr. Carlucci for referring this patient to me for study.

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ANNOUNCEMENT OF THE 1948 MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Thirtieth Annual Meeting of the Association for the Study of Internal Secretions will be held in the Palmer House, Chicago, Illinois, June 18 and 19, 1948.

The scientific sessions will be held in the Red Lacquer Room and registration will be on the fourth floor just outside the Red Lacquer Room. The Annual Dinner will be held in the same room on Friday, June 18th at 7 P. M. and will be preceded by a cocktail party, the location of which will be announced later. The Council will meet at 2 P. M. Thursday, June 17th.

All members of the Association who plan to attend the Thirtieth Meeting are urged to make their reservations at once with the Palmer House, stating the time of arrival and how long they plan to remain in Chicago.

Announcement of Awards and Fellowship of the Association

Nominations for Awards

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1948.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori. No award was made in 1943. No age or special limitation is stipulated by the donor of the award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or pre-clinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman and in 1947 to Dr. Choh Hao Li. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first award of the Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947. The fellowship was founded in order to encourage investigation in the field of endocrinology rather than as an award

for work done. The amount of the fellowship is $2,500.00 annually. The nominee must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed the requirements for their Ph. D. or M. D. degree. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals; submit a program of proposed study; indicate one or more institutious where the proposed program will be carried out; submit statement of approval from the investigators with whom he proposes to conduct his research; serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Postgraduate Course in Endocrinology

The Postgraduate Committee of THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, under authority of its Council, announces a course of lectures and demonstrations in CLINICAL ENDOCRINOLOGY to be held in LOS ANGELES at the BILTMORE HOTEL, FEBRUARY 23, to 28, 1948, inclusive.

The faculty will consist of the most prominent investigators and clinical endocrinologists in the various branches of the medical sciences in the United States and Canada.

It is the intent of the Committee that this course be a practical one of interest and value to both the GENERAL PRACTITIONER AND THE SPECIALIST.

A fee of $100 will be charged for the entire course and the attendance will be limited to 100. Registration will be in the order of checks received and will close on February 1, 1948. Should there be an insufficient number of applicants to warrant the course, the registration fee will be immediately refunded in full.

Please make your application on your letterhead and forward, together with your check payable to THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, to DR. E. KOST SHELTON, CHAIRMAN of the POSTGRADUATE COMMITTEE, 921 WESTWOOD BOULEVARD, LOS ANGELES 24, CALIFORNIA.

Since satisfactory hotel accommodations are still difficult to procure on short notice in Los Angeles, especially during the winter season, it is suggested that all applicants MAKE THEIR RESERVATIONS EARLY.

SOME LARGE HOTELS IN THE METROPOLITAN AREA OF LOS ANGELES:

Alexandria	Chapman Park	Lankershim
Ambassador	Gaylord	Mayflower
Biltmore	Hayward	Town House

AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Toronto, Canada, May 6th, 7th, 8th, 1948 providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than February 1st, 1948. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association. This will not prevent its further publication, however, in any Journal selected by the author.

T. C. DAVISON,
Corresponding Secretary

Abstracts of

CURRENT ENDOCRINE LITERATURE

Editor; D. A. McGINTY. *Collaborators:* A. R. ABARBANEL, F. N. ANDREWS, B. L. BAKER, F. A. DE LA BALZE, ISRAEL BRAM, R. A. CLEGHORN, RUCKER CLEVELAND, C. D. DAVIS, ANNA FORBES, M. B. GORDON, H. S. GUTERMAN, M. M. HOFFMAN, R. G. HOSKINS, C. D. KOCHAKIAN, H. S. KUPPERMAN, H. L. MASON, JANET W. MCARTHUR, THOMAS H. MCGAVACK, A. E. MEYER, K. E. PASCHKIS, A. B. PINTO, J. R. REFORZOMEMBRIVES, E. C. REIFENSTEIN, JR., G. G. RUDOLPH, L. T. SAMUELS.

PANCREAS

STAINSBY, W. J. AND J. A. COLLINS, JR. Diabetes mellitus. An analysis of 250 cases and a discussion of simplified procedures for regulation. *Pennsylvania M. J. 50* (8): 808–811 (1947).

An analysis of 250 consecutive cases of diabetes admitted to the Geisinger Memorial Hospital showed that the main reasons such patients were unsatisfactorily regulated were: (1) insufficient diabetic instruction; (2) too complicated a dietary and insulin regime. Experience has shown that a simple diet is satisfactory for the regulation of most cases and it may be quite similar to that taken prior to the development of diabetes. The main point is to take approximately the same amount of calories daily with the same proportions of carbohydrate, protein, and fat. The same simple procedures apply to the use of insulin, using single injections of protamine zinc insulin whenever possible and simple mixtures of protamine zinc insulin and crystalline insulin for most of the others. For severe cases of diabetes two injections of insulin each morning, one of protamine zinc insulin, the other of an intermediate insulin, such as globin insulin, have been found most practical. Mild hyperglycemia in the absence of ketosis and unfavorable symptoms is in no way harmful to patients. Insulin reactions in the elderly are dangerous and should be avoided as much as possible.—(Authors' Conclusions)—*I.B.*

WOOD, M. N. Chronic peptic ulcer in 94 diabetics. *Am. J. Digest Dis. and Nutrition. 14* (1): 1–11 (1947).

The author studied 94 diabetic patients with chronic peptic ulcer. He noted that the average age of these patients was greater than the age of the average ulcer group, and there was a relatively high incidence of females with ulcers in his study. The initial ulcer symptoms were vague and atypical, especially in those patients with diabetes of long standing. 21 of the patients had no free hydrochloric acid in the fasting gastric contents. The high incidence of ulcer complications (hemorrhage, perforation, and obstruction) was suggested as being due to the vagueness of symptoms which masked the diagnosis of the ulcer and the duodenal obstruction. Arteriosclerosis was considered a contributing factor to bleeding from the peptic ulcers studied. Therapy of these patients was directed primarily toward relieving the ulcer symptoms, with insulin added to control the hyperglycemia and glycosuria.—*H.S.G.*

GENERAL

HANSON-PRUSS, O. C. Thiouracil in the treatment of leukemia. *Proc. Soc. Exp. Biol. and Med. 64* (4): 496–500 (1947).

Six patients with chronic myelogenous leukemia and one with acute myeloblastic leukemia were treated with thiouracil. The average daily dose was 1.5 Gm., and one patient received a total of 359.3 Gm. over a 10 month period. Thiouracil was well tolerated by every patient and had no effect on the total circulating white cell count, nor on the differential white cell picture, red cell elements, hemoglobin or platelet values or the bone marrow pattern. At the dosage given, the drug had little influence on the B.M.R., serum cholesterol, bone marrow pattern or myeloid dysfunction and did not modify the clinical course of the disease. The author concluded that thiouracil has no value as an adjunct in the treatment of myelogenous leukemia.—*F.N.A.*

LIKINS, C. H., JR., E. P. SCOTT, AND N. I. HANDELMAN. Laurence-Moon-Biedl syndrome. *Am. J. Dis. Child. 73:* 195 (1947).

The authors present the case histories and physical findings of a 10½-year-old white girl with Laurence-Moon-Biedl syndrome, and in addition that of her 18-month-old brother who also had this condition. The authors briefly review the literature on this disorder. The characteristic symptoms are obesity, retinal degeneration, general hypoplasia, polydactylism and mental retardation. Frequently associated are nystagmus, strabismus, deafness and syndactylism. A familial tendency has been reported in 80 per cent of the cases. The diagnosis depends mainly on clinical observation of the abnormalities. The most acceptable concept as to etiology is that the syndrome is a hereditary developmental disturbance due to recessive mutations of two genes in the same chromosome. Among the other causal factors which have been suggested are endocrine imbalance, and cerebral aplasia from hydrocephalus. The only consistent laboratory finding has been a low basal metabolic rate. Thyroid medication has been of some value in reducing the weight of these patients, but no other endocrine therapy has been particularly helpful. The patients described by the authors received no treatment.—*E.C.R., Jr.*

WETZEL, N. C. The baby grid. An application of the grid technique to growth and development in infants. *J. Pediat. 29:* 439 (1946).

The author has adapted to individual infants a chart for direct reading of the quality of growth and development during the first three years. This chart follows the principles previously described by him and referred to as the Grid Technique (*J.A.M.A.* 116: 1187 (1941); *J. Pediat.* 22: 82, 208, 329 (1943). The chart contains a channel on which the measurements of the baby's weight and length can be placed, and from which the developmental level, the motor-mental development, and the caloric intake can be read. Tables are also provided on which the chest circumference and the head circumference can be noted. An example of the application of the Baby Grid to the development of an infant is given. The author states that the Baby Grid has been designed to pictorialize the growth and development of a given infant during its first three years, and to make this and the quality of growth evident at a single glance.—*E.C.R., Jr.*

ERRATUM

Through an oversight, the names of the new officers for The Association for the Study of Internal Secretions did not appear in the July and subsequent issues of the *Journal of Clinical Endocrinology*. A list of the officers for 1947-1948 appears in this issue of the Journal (page iv).